Focus on
REPRODUCTION

European Society of Human Reproduction and Embryology // SEPTEMBER 2010 //

Sperm quality

The clinical implications of environmental factors

- ESHRE news
- A record-breaking annual meeting
- Tests of ovarian reserve reviewed

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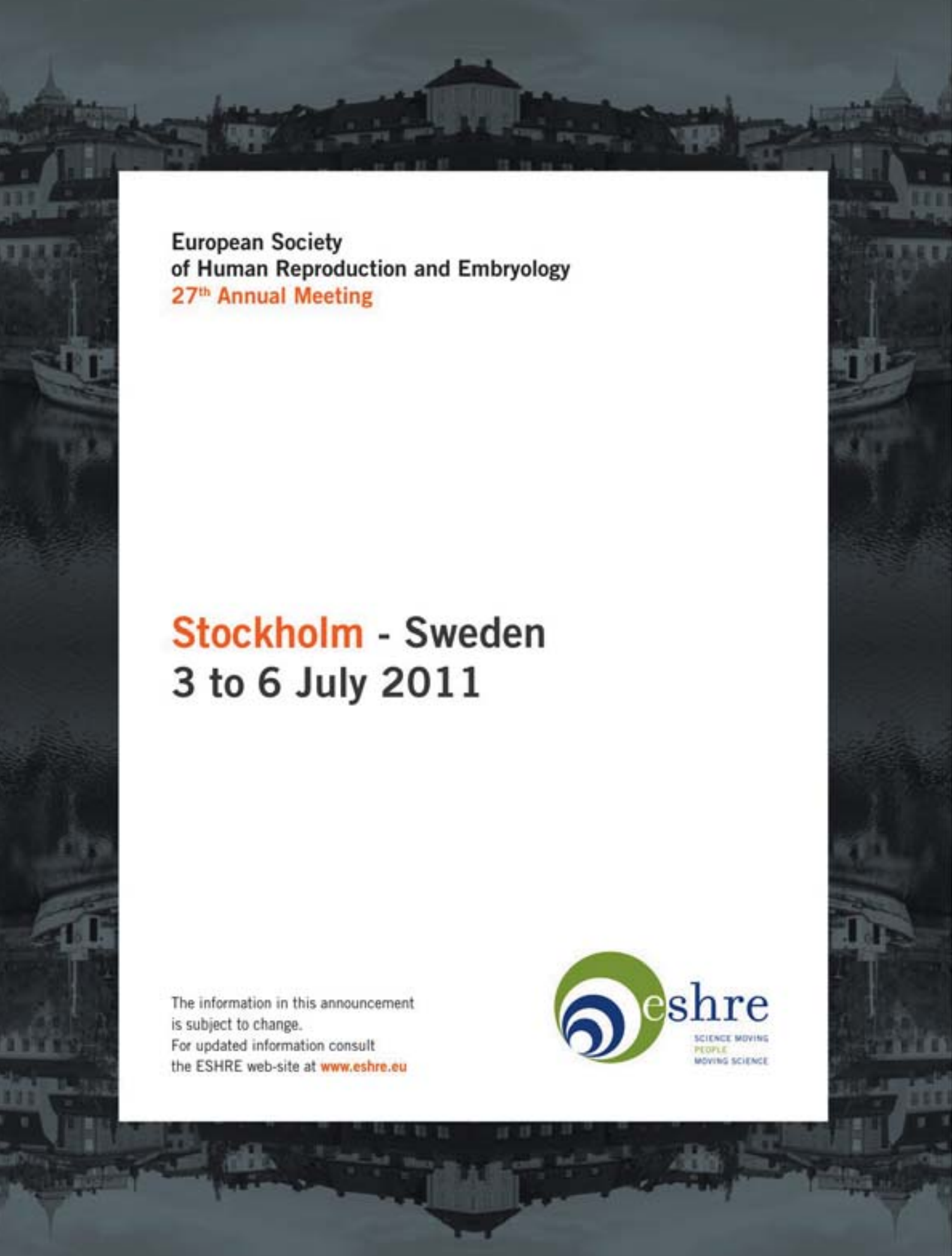
SCIENCE MOVING PEOPLE MOVING SCIENCE



European Society
of Human Reproduction and Embryology
27th Annual Meeting

Stockholm - Sweden
3 to 6 July 2011

The information in this announcement
is subject to change.
For updated information consult
the ESHRE web-site at www.eshre.eu

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SEPTEMBER 2010

Focus on
REPRODUCTION

Chairman's introduction

After the success of our annual meeting in Rome and some well-deserved summer holidays, here we go again with a new issue of *Focus on Reproduction*.

The annual meeting was as usual a momentous scientific event, with 13 pre-congress courses and 70 sessions of lectures. I am sure that, despite their different professional interests, all the members who had the opportunity to attend filled their schedules with presentations to follow.

The meeting broke several ESHRE records, particularly in the attendance of more than 9000 registered participants from 109 countries, reflecting the increasing appeal of our Society and its activities even outside Europe. Media coverage of the event, even in non-specific publications, was very satisfactory. We were also pleased to ensure the collection of untouched food during the meeting; we avoided the waste of more than 500 kilos, which was distributed to charity institutions.

These figures certainly make us feel extremely proud, but they don't curtail our wish for further improvement. Our Central Office - which I would like to thank on behalf of all ESHRE members for its commitment - is already working on our next annual meetings in Stockholm (2011) and Istanbul (2012). After all, records are made to be broken!

As a consequence of ESHRE's conspicuous investment in education, a variety of workshops and Campuses on different topics are being organised for the last few months of 2010 and for the first half of 2011. As usual they will provide participants with unique opportunities to update and increase their knowledge and skills.

ESHRE is also making an effort to broaden its field of activity to provide better answers to the different issues raised not only by ART professionals but also by patients and institutions. Because of its expert base, ESHRE is establishing itself as a reliable and competent consultant for a variety of institutions at national and international level. The involvement on the SOHO V&S (Substances of Human Origin Vigilance & Surveillance) project in partnership with the EU is one such example. Less scientific, but equally important, are the aspects of ART being investigated by the newly established Task Force on Management of Fertility Units to provide a useful support to the management activities of centres. Partnerships are being established and activities are under way - so prepare to be surprised!

Luca Gianaroli
ESHRE Chairman 2009-2011

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Arrivederci Roma
Hej Stockholm

Kersti Lundin, local chair of next year's annual meeting, previews what's in store in Stockholm

ESHRE's 27th annual meeting next year will take place in Stockholm, the capital city of Sweden which is home to approximately 1 million inhabitants. It is a beautiful city, situated on a number of islands and with many green spaces. Indeed, throughout 2010 Sweden's capital will be celebrated as Europe's first Green Capital, a title conferred by the European Commission. Stockholm has taken clear and effective measures to reduce noise pollution - and 95% of its population now lives less than 300 metres from green areas. Many years of effort lie behind the award - efforts that have now turned Stockholm into a sustainable, growing metropolis.

As befitting a city with such contemporary and historic attractions, Stockholm has a large hotel capacity, with more than 12,000 beds in its central area alone. It has a well functioning transport system, with metro, buses and local trains.

We are expecting more than 8000 delegates in 2011, but Stockholm has a solid track record for hosting large events - indeed, the congress of the European Society of Cardiology, planned to take place in Stockholm in early September, was expecting more than 25,000 participants, and the venue itself - 'Stockholmsmässan (Stockholm International Fair and Trade Center)' - will comfortably accommodate ESHRE's annual meeting, even with 8000+ in attendance. The conference centre is situated in Älvsjö, just south of the city. The local train, which leaves every 15 minutes, will take you from Stockholm Central station to Stockholmsmässan in just nine minutes.

KERSTI LUNDIN: 'THE HOTELS ARE ALREADY PRE-BOOKED, THE SCIENTIFIC PROGRAMME IS MORE OR LESS FINISHED, THE SOCIAL PROGRAMME IS IN PLACE . . . .'

Scientific programme

The scientific programme opens on Sunday morning (3rd July 2011) with a wide selection of precongress courses (no fewer than 17 in total). As in the past years, delegates can take advantage of a combined registration which includes participation in both precongress courses and the main programme, giving good value for money.

Monday morning (4th July) begins with an intriguing keynote lecture on aneuploidy in humans - what we know and what we wish we knew. Following that, we continue with three days packed with ESHRE's usual hot topics, presented as invited sessions, debates and peer reviewed, selected oral communications, providing both state of the art as well as the latest data in their respective areas.

Abstracts can be submitted any time until 1st February 2011. You can find more information about abstract topics and submission guidelines on ESHRE's website www.eshre.eu, but remember that abstracts can now only be submitted online.

Social programme

The opening ceremony takes place in the congress centre on Sunday evening. As usual, the programme of the ceremony will be a surprise, but we can promise music and dance followed by a welcome reception with food and drinks in the exhibition hall. This is a good time to meet your

The Vasa museum, venue for next year's congress party.

Abstract submission policy

Full details of ESHRE's abstract submission policy are on the ESHRE website (www.eshre.eu), but please note:

- All abstracts must arrive at ESHRE's Central Office no later than 1st February 2011.
- Abstracts should be submitted in English only.
- Any person submitting an abstract can only be the first author for one abstract.
- The material presented should be unpublished and original material, which has not yet been presented in any other meeting.
- All abstracts will be refereed 'blind'.
- Authors are requested to indicate their preference for oral and/or poster presentation on the abstract submission form. The decisions of the selection committee are final.

colleagues while strolling around and to meet our industrial sponsors, who as ever will be exhibiting their latest products.

The congress party will be a spectacular event taking place in the Vasa museum. The museum is centred around the fantastic Vasa ship, which sank in the middle of Stockholm harbour in 1628 when leaving on its maiden voyage. After more than 300 years it was salvaged from the water and restored. The ship is decorated with more than 100 carvings. The museum is an amazing exhibition of the ship itself and of daily life on board. Here you can enjoy food and drinks while listening to guides recounting the ship's history; a live music and dance party follows.

But while in Stockholm, don't miss the opportunity for a bit of sightseeing as well. Take a walk through the small winding streets of the old town lined with craft shops, art galleries and cafés. In the old town you will also find the Royal Palace with the changing of the guard. Try to visit the City Hall, where the Nobel Prize dinner takes place every December, or Skansen, which is the world's oldest open air museum. Stockholm is, of course, also famous for its archipelago of 30,000 islands and skerries. It is very easy to take a boat to one of the more far off islands, for lunch or just a walk.

And, if you want to use your stay to see a bit more of Sweden, you can head to the north - where the sun shines all day and night in the summer - or to the west coast with its beautiful archipelago (quite different from the islands on the east coast). Or you can travel to the Kingdom of Crystal (Glasriket) in the south-east of Sweden, to visit the glass furnaces. You'll find everyday glass and art glass of world-class quality, and will be welcome to step up to the glass furnaces to see the glass being created, and perhaps buy some to take home. And for those of you wanting some exercise, Sweden can also offer more than 300 golf courses.

So, in short, the hotels are already pre-booked, the scientific programme is more or less finished, the social programme is in place, and we are all set to welcome you to Stockholm from 3-6th July 2011. Mark your diaries now, and keep up to date with further information on the ESHRE website.❑

While Stockholm is known the world over as the 'Venice of the North', in 2010 it has been designated Europe's first Green Capital.

More than 9000 take the road to Rome

A congress which broke all ESHRE records

With more than 9000 in attendance (just) and an exhibition area looking more like Las Vegas than the Royal Society of Medicine, this was the year that ESHRE's annual meeting - like Julius Caesar 2000 years before - crossed the Rubicon and stepped into the unknown territory of 'major event'.

Rome 2010 was a momentous occasion for ESHRE, a congress which broke every record of every previous event and left far behind the cosy meetings of its formative years: more abstracts, more delegates, more journalists, more electronics . . . and more shuttle buses.

Gayle Jones from Melbourne delivers the inaugural Human Reproduction lecture.

But, as ever, this was also a meeting defined by ESHRE's traditional mix of science and clinical results, with high spots on the agenda right from the first moments of the opening keynote lectures. By Wednesday evening, almost 300 invited and submitted oral presentations had been made in 70 oral sessions, and 579 posters published, all selected from an unprecedented submission of more than 1500 abstracts. As a prelude to the meeting, more than 1600 took part in the 13 precongress courses staged by ESHRE's SIGs and Task Forces, while at the finale more than 100 specialists joined in a celebration

of 20 years of PGD, including most of those who had shaped its formative history.

This year, the opening keynote presentation was the inaugural *Human Reproduction* lecture, whose subject and speaker were based on the number one paper published in *HR* between January 2008 and March 2009 according to downloads in the first six months after publication, a measure which correlates closely with eventual citations. This year, the honour fell to Gayle Jones from Melbourne, whose presentation on the promise of a science-based marker of blastocyst competence laid down a bearing of IVF's present location. She described the combination of microarray gene profiling and DNA fingerprinting as a 'powerful tool' in the selection of the single viable blastocyst likely to implant; the transition from 'subjective' non-dynamic morphological embryo selection to a standardised objective assessment is now well under way, she said.

This transition was further underlined by results from ESHRE's own PGS Task Force of a pilot study of polar body analysis by array CGH as a means to finally crack preimplantation aneuploidy screening. Unlike the FISH technology now found wanting in all previous clinical trials, array CGH can evaluate the status of all 23 chromosomes - and, unlike blastomere analysis, is not compromised by mosaicism. This proof of principle study - as a fuller report on page 13 indicates - confirmed the 226 polar body results (taken from both polar bodies) as accurate in 89% of the analyses; these were all performed within 12 hours, thereby making real-time transfer comfortably possible. Former ESHRE chairman and co-ordinator of the PGS Task Force Joep Geraedts said that immediate priorities were to publish the results and push forward to a randomised clinical trial. However, the proof-of-principle results, he warned, were no proof of clinical applicability.

Such a view - that a small pilot study in ART is no substitute for a full clinical evaluation - was a recurring theme in the second of the opening keynote lectures, in which ethicist Wybo Dondorp from the University of Maastricht called for greater responsibility in research in reproductive medicine. 'Responsible innovation requires that potentially risky technologies are the subject of research,' he said, 'ideally proceeding through preclinical investigations, clinical trials and follow-up studies.' Society at large must accept responsibility for this, but, at the professional level, Dondorp proposed that ESHRE itself 'is equipped to take a lead' in establishing public trust and accountability through its expertise, guidance and training.

In the second keynote lecture ethicist Wybo Dondorp called for greater responsibility in research in reproduction.

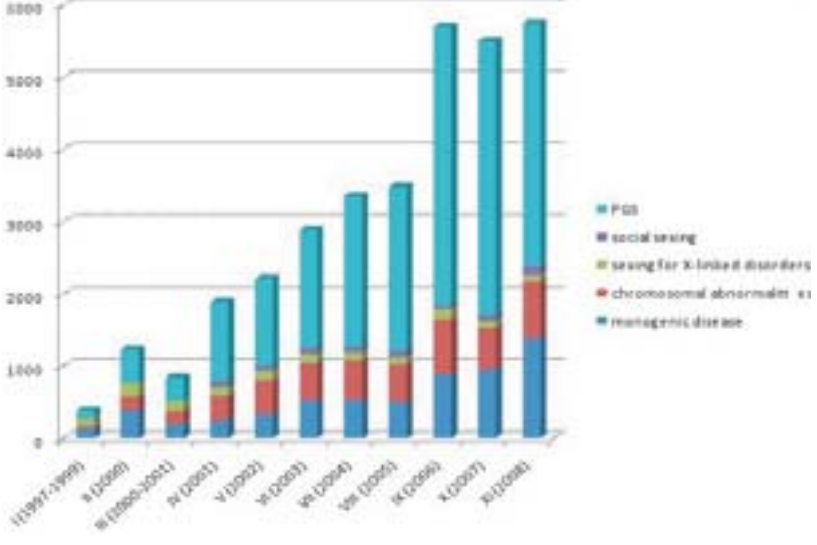
Completing her term in Rome as chairman of the PGD Consortium was the London geneticist Joyce Harper, who is replaced by Gary Harton, now working at Reprogenetics in New Jersey, USA. This year's report was a provisional summary of the Consortium's 11th annual data collection, reflecting PGD activity for 2008. Despite publication in 2007 of the clinical trial by Mastenbroek et al showing a negative effect of PGS on ART outcome (as well as downbeat recommendations from the ASRM, British Fertility Society and ESHRE), PGS was still dominating that activity in 2008, with 60% of

In Rome Gary Harton took over from Joyce Harper as chairman of the PGD Consortium. Results from the Consortium's XIth data collection were presented in Rome, showing, below, that aneuploidy screening remains the greatest application of PGD, albeit at a rate which was just decreasing in 2008.

cycles registered for aneuploidy screening and 37% for PGD. Cumulatively, said Harper, the Consortium's database represents a 'huge number' of cycles, with almost 190,000 embryos biopsied and 6329 clinical pregnancies, 74% of which were singletons. It seems likely, she added, that in the foreseeable future biopsy will concentrate on the polar bodies or blastocyst (most likely with vitrification), molecular PGD may be performed by PCR or whole genome amplification with or without SNP/CGH array, and PGS - pending a clinical trial - will not be done with cleavage stage embryos, nor with FISH, but with CGH on polar bodies or trophectoderm cells.

An update on ovarian tissue preservation before cancer treatment presented by Claus Yding Andersen from Copenhagen revealed that 14 children worldwide have now been born following transplantation of the frozen/thawed tissue, some of them from natural conceptions. In Denmark alone, where Andersen's laboratory at Rigshospitalet is the only centre offering the service, a total of 16 women have had transplantations on 22 occasions, six of them twice, and three children have been born to two women (with a further clinical pregnancy). There have been two unsuccessful pregnancies and five non-conceptions. 'We're slowly getting there,' said Andersen, who described ovarian tissue cryopreservation as 'a valid alternative' to oocyte and embryo freezing in these cases. Its advantages, he added, are that the cryopreservation can be performed at short notice, that the functional unit of the ovary is preserved, and that a large number of follicles are available for future fertility restoration. Most cases in Denmark have been in patients with Hodgkin's lymphoma and breast cancer.

Embryo selection, mild IVF and single embryo



transfer were all recurring themes in the scientific programme, but a lively debate on the superiority of multiple natural cycle IVF over a single stimulated cycle and freezing was won by the latter. Defending the proposition, Human Fatemi from the VUB in Brussels proposed that triggering ovulation with a GnRH agonist in a stimulated GnRH antagonist single-embryo transfer cycle would remove the two major risks of IVF, multiple pregnancy and OHSS. Thus, the main advantage of a natural cycle - safety - can now be incorporated into the stimulated cycle without any compromise to results. Indeed, a review of all treatments in Australia and New Zealand between 2004 and 2007 (more than 34,000 women) found that transfer of single blastocyst in women under 35 years not only achieved the highest rates of live delivery (46.2%) but also the highest rate of 'healthy babies' when deliveries were measured as singletons of 2500 grams birth weight and without congenital complications (38.0%). A similar study of 4701 consecutive fresh cycles performed at Guy's and St Thomas's Hospital in London found (after

Food for thought

The registration fee at ESHRE's annual meetings includes refreshments at the morning and afternoon coffee breaks and lunch. As the number of participants increases, so does the challenge of providing enough food and drink for everyone, without encouraging waste. This year the ESHRE organisers agreed a deal with a local agency that all unused food was removed and delivered to local charities for consumption by their clients within two hours. On the final day of the congress more than 500 kilos were delivered to the charities.

adjustment for age) that clinical pregnancy rates increased with the number of eggs collected, but only up to six oocytes, after which results reached a plateau. A similar pattern was found for women having blastocyst transfer.

Two posters - both from Japan - describing the cryopreservation of a single and a small number of sperm cells proved extremely popular in the e-poster area. The former used the Cryotop vitrification system and cooled the strip in vapour of liquid nitrogen before submersion. The investigators, from the Kurashiki Medical Clinic in Okayama, found that best survival rates (63%) were when sucrose was used as the freezing medium. In the second, a small number of spermatozoa were placed in a non-biological container tray which, when put in a cryotube was also vapour-frozen before plunging in liquid nitrogen. Fifty motile spermatozoa were cryopreserved using ten freeze containers. The post-thaw recovery and motility rates were 100% and 54% respectively. Both methods were described as easy to use.

Another poster, presented by Cochrane collaborators from Australia and New Zealand, found in a meta-analysis of 32 studies involving almost 2700 male patients that taking oral anti-oxidants improved total sperm motility and IVF pregnancy rate with a pooled odds ratio of 3.89 ($p<0.00001$).

Sixteen studies were featured in the press programme, which this year attracted 95 journalists, including 35 from Italy. There was high interest in the ability of anti-Mullerian hormone levels to predict the timing of the menopause, in ESHRE's PGS pilot study of array CGH, and in the potential of a simple, non-invasive, prenatal test for chromosomal abnormalities, including Down's syndrome. The last, a proof-of-principle study presented by Suzanna Frints from Maastricht University Medical Centre, used multiplex ligation-dependent probe amplification (MLPA) to detect fetal DNA in the blood of women a few weeks pregnant.

One award-winning study featured in the press programme may also have implications for all clinics in Europe now faced with EU requirements for viral screening at each ART cycle. In Ireland, where the EU's three tissue and cell directives have been strictly adopted, that requirement is for HIV1 and 2 and hepatitis B and C screening to be carried out within 30 days of the start of each cycle. But

The natural or the stimulated cycle? In the first debate of the congress Human Fatemi from the VUB in Brussels argued that the stimulated cycle can now achieve the same degree of safety as the natural cycle, without any reduction in results.

Ciara Hughes from Dublin won the Clinical Science Poster Award for an analysis of virology screening in ART.

embryologist Ciara Hughes from Dublin, who analysed screening results over a ten-year period in 1023 negative couples (who had returned to her clinic for testing after a 180 day quarantine of their surplus frozen embryos), found no seroconversions on re-testing. She described the risk of seroconversion in ART patients as 'negligible', adding: 'Since the introduction of the new testing requirement in Ireland, we have carried out 17,494 viral screen tests either before therapy or within 30 days of egg collection and have not come across a single seroconversion. Assisted reproduction is not the same as organ donation or blood transfusion.'

While the ART sector was only marginally consulted in the construction of the original directive, the ESHRE information session in Rome heard that ESHRE will take part as a society of reference in several work packages of the European Commission-funded Substances of Human Origin - Vigilance and Surveillance (SOHOV&S) project, including the reporting of serious adverse events and reactions in ART. Project leader Dr Deirdre Fehily said its overall objective is to help in the establishment of vigilance and surveillance systems through standardised inspection and certification, and a uniform model of reporting and investigating.

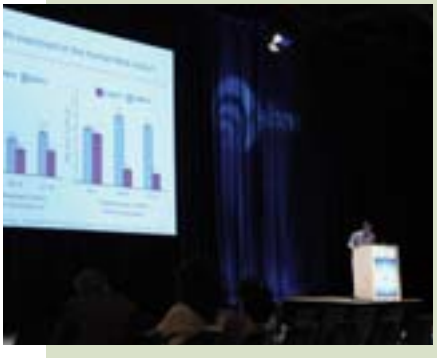
Simon Brown
Focus on Reproduction

ESHRE 2010: award-winning presentations

Clinical Science Award for Oral Presentation
O-054 Materno-fetal cardiovascular complications after oocyte donation in Turner syndrome: a very high-risk pregnancy
Fénichel P, Letur H, Chevalier N, Lelannou D. Ohl J, Cornet D, Chalas-Boissonnas C, Jonard-Catteau S, Greck-Chassain TH, Cedrin-Durnerin I, France

Clinical Science Award for Poster Presentation
P-315 Is performing viral screening within 30 days of oocyte collection justified?
Hughes C, Emerson G, Grundy K, Kelly P, Mocanu E, Dublin, Ireland

Basic Science Award for Oral Presentation (pictured right)
O-077 The cleavage stage embryo is the cradle of chromosomal rearrangements
Vanneste E, Voet T, Melotte C, Vandendael T, Declercq M,; Vervoort C, Debrock S, Fryns JP, D'Hooghe T, Vermeesch JR, Leuven, Belgium



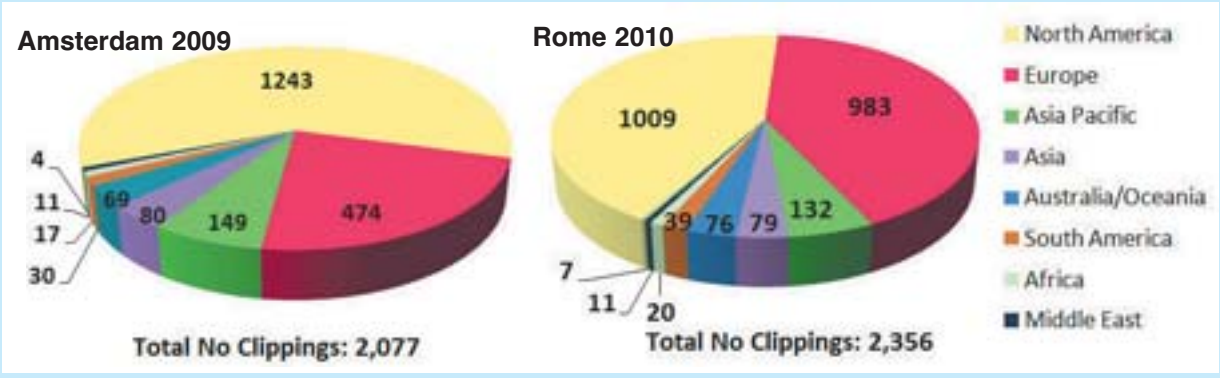
Basic Science Award for Poster Presentation
P-193 MicroRNA-135a regulates early embryo development through mediating expression of E3 ubiquitin ligase seven in absentia Homolog 1 (SIAH1)
Leung CON, Pang RTK, Liu WM, Lee KF, Yeung, WSB, Hong Kong

Fertility Society of Australia Exchange Award (pictured left)
O-192 BMP signalling in the human fetal ovary is developmentally-regulated and promotes primordial germ cell apoptosis
Childs AJ, Kinnell HL, Collins CS Hogg K, Bayne RAL, Green SJ, McNeilly AS, Anderson RA, Edinburgh, United Kingdom

Nurses Award (pictured right)
O-050 Assisted reproductive technology nursing: Positioning Australian research in the global context
Applegarth J, Dwyer T, Moxham L, Rockhampton, Australia

ART Laboratory Award
O-156 Snp array-based combination of copy number and genotype analyses to determine chromosomal imbalances in human blastomeres
Uum van CMJ, Stevens SJC, Dreesen JCFM, Drusedau M, Smeets HJM, Hollander-Crombach HTM, Geraedts JPM, Engelen JJM, Coonen, E, Maastricht, The Netherlands

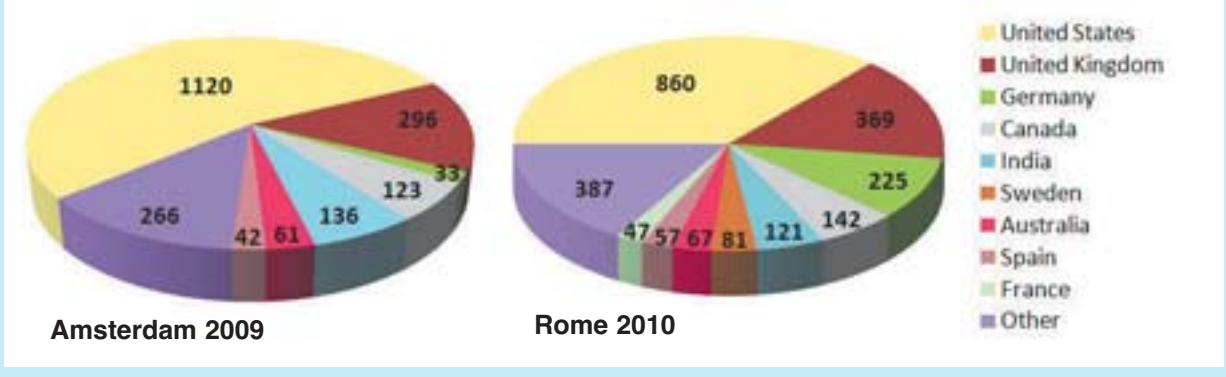
Records also broken in the Rome press office



News clippings reporting ESHRE presentations in Rome (right) increased by 14% over Amsterdam 2009 (left).

ESHRE's press activities in Rome topped all records in terms of journalist attendance, total media coverage, European media coverage and number of clippings.

- Overall, press coverage was more evenly distributed and less reliant on English speaking media, particularly UK. Coverage almost reached a 50% EU share (see below), with prominent reports in Swedish national newspapers (*Dagens Nyheter*, *Aftonbladet*), German newspapers (*Sueddeutsche Zeitung*, *die Welt*), UK (*Daily Telegraph* and *Times*), and many more.
- There was also quite extensive coverage in broadcast media -national Belgian radio, Swedish national TV (SVT 1), UK (BBC Radio), US (CNN) and Australia (ABC News).
- Although the number of press releases decreased from 18 in Amsterdam to 14 in Rome, the number of news clippings increased from 2077 to 2356, a total increase of almost 14% in coverage (detected online).



High viewing figures for electronic posters

A record total of 1539 abstracts were submitted for ESHRE 2010, of which 239 (15.5%) were selected as oral presentations and 579 as posters. Authors were given the option of poster boards as well as electronic publication in the poster village; 147 (25%) chose the latter option.

A remarkable number of posters were viewed electronically each day in Rome - 5212 on Monday, 6415 on Tuesday, and 3582 on Wednesday, Most viewed were posters in andrology, followed by embryology and reproductive genetics. Most frequently viewed individual posters were P-004 Cryopreservation of single spermatozoa using CryoTop, and P-006 Oral anti-oxidant use for male partners of couples undergoing fertility treatments.

A new chairman for national representative committee

Following the unexpected resignation of the UK's Peter Braude as chairman of the Committee of National Representatives (CNR), ESHRE's Executive Committee has appointed the Society's Past Chairman Joep Geraedts as interim chairman of the CNR. The Committee considered the appointment of an Executive Comittee member to fill the vacated chair as the most practical solution to the immediate and - as Peter Braude indicated - the longer term problem of the CNR's interaction with the Committee. ESHRE's Chairman Luca Gianaroli reaffirmed that the CNR's primary role is to advise the Executive Committee and agreed that - in the short term at least - an Executive Committee member as chairman of the CNR seemed an appropriate solution.

In order to strengthen liaison between the two committees, the Executive Committee in Rome agreed that the chairman of the CNR should inform members of any relevant developments, invite fellow members to contribute to forthcoming Executive Committee meetings, and produce a brief quarterly news update for the CNR.

The election of new national representative members of the CNR is due in 2011, and the nomination process will begin later this year. Once the nominated candidates are ratified, they will seek election through a vote which should be completed before next year's annual meeting. Details of the nominees will be published in *Focus on Reproduction*.

New PGD Consortium guidelines ready for print

Three new best-practice guidelines developed by the PGD Consortium have undergone final editing and been submitted for publication in *Human Reproduction*. The three guidelines are on

- organisation of a PGD centre
- FISH-based PGD
- amplification-based PGD

The draft of a fourth best-practice guideline - on polar body and embryo biopsy - has just completed its four-week consultation on the ESHRE website.

The four guidelines, which have been developed by a PGD Consortium working group according to ESHRE's own guideline manual, are a detailed update to the Consortium's initial PGD and PGS guidelines, which were published in *Human Reproduction* in 2005.

'The new guidelines have been developed as a set which, taken together, will form a complete best-practice compendium,' said working group chairman Gary Harton.

ESHRE to host workshop at leading European Health Forum

ESHRE will host a workshop on 'Individual choices in reproductive health' at the European Health Forum Gastein on 6th October. The event, which was founded in 1998 as a European health policy conference, has today become Europe's leading gathering of politicians, policy-makers, consumer groups and experts in health administration from government, science and academia. The 600+ participants usually include the EU Health Commissioner, national health ministers and member state officials, as well as administrators from NGOs.

ESHRE's workshop, which takes as its theme the variability of legislation and reimbursement policy in Europe in assisted reproduction, will reaffirm ESHRE's position that treatments of proven benefit should be available throughout Europe, irrespective of income, place of residence or marital status.

The ESHRE programme will be composed of four presentations, each representing a particular perspective on the theme: from the patient, the drug industry, and the politician (presented by Isabel de la Mata Barranco, a Principal Adviser to the European Commission [DG Sanco] with a special interest in public health and risk assessment). Luca Gianaroli will present the place of ART in society today, Dr Joan-Carles Arce from Ferring the industry perspective, and Clare Lewis-Jones, chair of Fertility Europe, will speak on behalf of the patient, with particular emphasis on cross-border care. The overall theme of this year's Forum is 'Ready for the future?' with subtopics on healthy ageing, EU action and local partnership, and personalised medicine, in which ESHRE's workshop is programmed.❑

Polar body analysis by array CGH proves feasible in ESHRE proof-of-principle study

Planning now begins for a multicentre randomised trial

An ESHRE pilot study designed to test the feasibility of polar body analysis by array CGH as a means of preimplantation genetic screening (PGS) has met its clinical endpoints: the study, the first critical assessment of 23 chromosome testing of both polar bodies with array CGH, showed that analysis can be completed within 12-13 hours (thereby allowing for fresh transfer), and that the reliable identification of the chromosomal status of an oocyte is possible in almost 90% of attempts.

Presenting the results of the study in Rome, Joep Geraedts, chairman of the PGS Task Force - which designed and conducted the study - said that the results justify progress to a multicentre randomised trial. Planning and design, he added, will begin later this year, with a view to completion later in 2011.

All previous RCTs in PGS, said Geraedts, have proved disappointing, with the FISH technology unable to test all chromosomes and the biopsied blastomere unlikely to represent the entire embryo because of mosaicism.

The advantage of polar body biopsy, as incorporated in the ESHRE study, is that there are at this stage no multiple cells to be mosaic and that the biopsy is not such an invasive procedure. Moreover, because the developing embryo is not affected, polar body biopsy is allowed in countries which outlaw embryo screening, such as Germany, Austria and Switzerland.

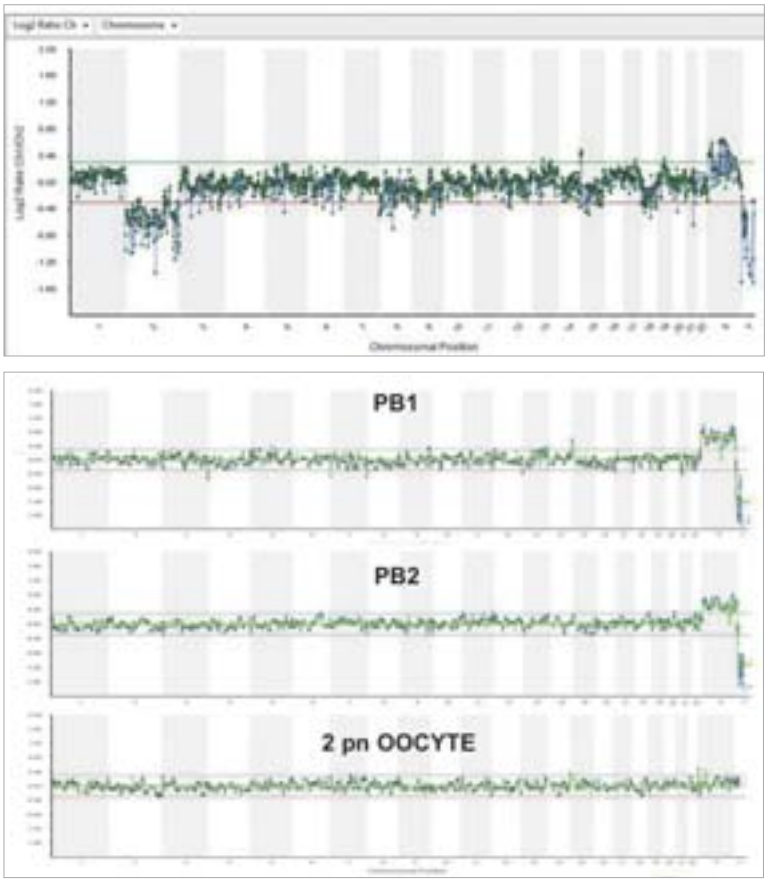
The study was conducted in two centres in Bonn and Bologna in 42 cycles in which all metaphase II oocytes were fertilised by ICSI. Both polar bodies were biopsied simultaneously - a skilled technique, said Geraedts - but analysed separately for aneuploidy using 24sure technology supplied by BlueGnome of Cambridge, UK. The average age of the 41 patients was 40.0 years, and they each produced an average of 5.5 zygotes, a total of 226.

DNA could be amplified in 421 of the 452 biopsied polar bodies (93%); results were obtained for both polar bodies in 191 cases (85%). From these it was predicted that 43 (23%) of the corresponding oocytes were euploid and 148 (77%) aneuploid.

In the 140 non-transfer cases concordance was determined by matching 24sure results from each polar body with those from the corresponding oocyte. In 89% of these cases the ploidy status appeared to be concordant.

'With chromosome errors being the predominant cause of non-viability of the embryo, we hope this approach will in future improve results in assisted reproduction,' said Geraedts, particularly in women of an older maternal age. However, he cautioned that these were results designed to do no more than prove feasibility; clinical efficacy would only be determined by the clinical trial.

Nineteen of the 42 cycles tested produced only aneuploid oocytes, leaving 23 with at least one euploid oocyte and the opportunity for embryo transfer. These transfers resulted in eight clinical pregnancies, an ongoing rate of 19% per cycle and 33.3% per transfer.❑



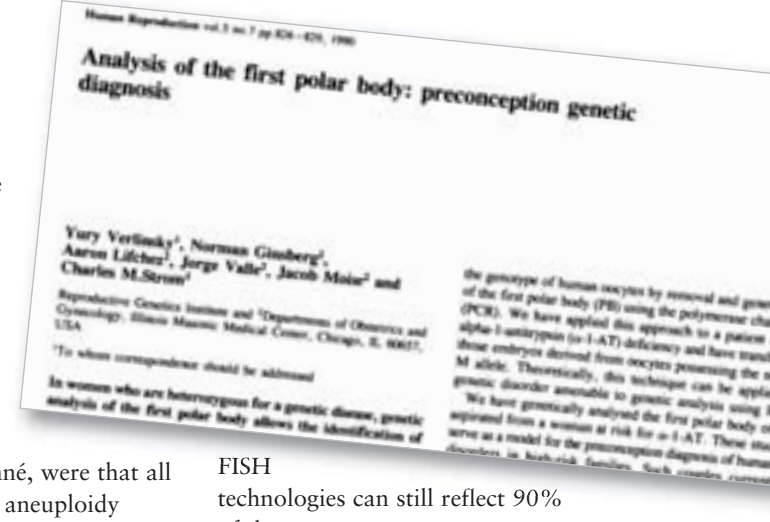
Loss or gain of one of the 23 chromosomes of the polar body is reflected in readings above or underneath the plotted lines. Above shows loss of a copy of chromosome 2 in a polar body. Below shows no abnormality in either polar body, which is concordant with the result of the 2pn oocyte.

// 20 YEARS OF PGD POST-CONGRESS COURSE //

The history makers review 20 years of PGD - and continue to shape its future

Participants in the '20 years of PGD' post-congress course held in Rome, many of whom had had a major part to play in PGD's history.

The cue for this 'celebration' of the first 20 years of PGD was the landmark paper in *Nature* by Handyside and colleagues in London reporting the first pregnancies following embryo biopsy and sexing by DNA amplification in two couples known to be at risk of transmitting recessive X-linked disease to their children. The technique, the paper explained, allowed the identification of unaffected female embryos and thus their selection for safe embryo transfer. The report, which described one unconfirmed and two confirmed pregnancies with normal female twins (in a series of five couples), was widely acknowledged as the beginning of successful PGD. This, however, was not the only celebratory paper of 1990.


Analysis of the first polar body: preconception genetic diagnosis

Yury Verlinsky[1], Norman Ginsberg[1], Aaron Lifchez[1], Jorge Valle[1], Jacob Moise[2] and Charles M.Strom[1]

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In women who are heterozygous for a genetic disease, genetic analysis of the first polar body allows the identification of

In this same year the late Yury Verlinsky and colleagues at the Reproductive Genetics Institute in Chicago reported in *Human Reproduction* that the genetic analysis of the first polar body would also allow the identification of those oocytes containing non-mutant maternal genes. Verlinsky described the case of a woman at high risk of transferring alpha-1-antitrypsin deficiency to her children and the identification of those oocytes showing no evidence of the mutant gene. Embryos from two oocytes containing the unaffected gene were transferred but no pregnancy was established. However, the accuracy of the polar body diagnosis was confirmed by polymerase chain reaction (PCR) analysis of an oocyte which failed to fertilise. Verlinsky thus added: 'Theoretically, this technique can be applied to any genetic disorder amenable to genetic analysis using PCR.'

The subliminal presence of Verlinsky was much felt at this meeting, for today, 20 years after his original report, the polar body (along with the blastocyst) seems now to be emerging as a cell of choice in PGD. Indeed, Joyce Harper, the outgoing chairman of the PGD Consortium, closed her historical review with a look to the future and foresaw biopsy concentrating on the polar body and blastocyst (with vitrification). 'We're moving away from the cleavage-stage embryo,' said Joyce. ESHRE's clinical trial of array CGH will also test the polar body as a blueprint for real-time transfer without freezing and without the confounding of embryo mosaicism.

It was also salutary to see the enormous technological landmarks of the past 20 years - through DNA amplification by PCR and chromosome analysis by FISH - suddenly supplanted by microarrays. Even the final slides of Santiago Munné, much of whose presentation was devoted to the 'optimized' application of FISH for preimplantation genetic screening, reported an error rate of just 1.8% with array CGH - in comparison to error rates of between 4 and 50% with FISH. The advantages of full chromosome analysis by array CGH, explained Munné, were that all chromosome types of aneuploidy could be detected, with results well within 24 hours, thereby permitting polar body or day 3 biopsy. 'Everyone's moving to arrays,' said Munné somewhat ruefully, while adding that the new 12-chromosome FISH technologies can still reflect 90% of the genome.

However, while progress has been the talisman of PGD technology over these past two decades, this celebration was also a reminder that there's much about PGD which hasn't

The reason why we do what we do

It is sometimes easy to forget why we do what we do in the lab each day. It's easy for patients to be no more than a name on a slip of paper, the biopsy schedule for another week. Of course, we are all thrilled when our 'patients' get pregnant, but in truth we rarely even know who our 'patient' really is, what they look like, where they are from - or how they arrived at our PGD clinic. Even more rare is seeing the fruit of our labour beyond day 3 of embryo development.

But all that changed for those of us lucky enough to be in Rome for our celebration of PGD post-congress course. In its effort to truly celebrate the history of PGD and how it has benfitted families, the organising committee invited two PGD patient families to discuss with us their success and failures.

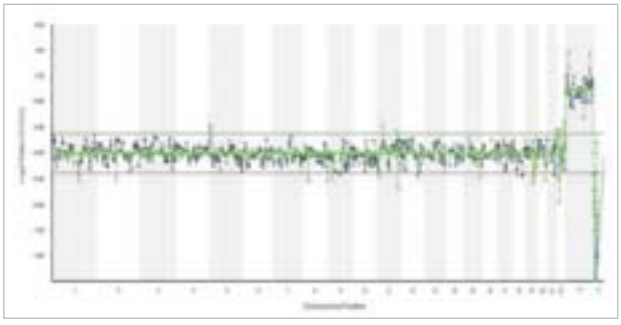
While the two invited families had very different stories to tell, and different ways of doing so, their message was the same - that PGD had changed their lives in ways they could not imagine, even in ways beyond having an unaffected child.

The first couple to speak, David and Linda Galloway from the USA, chose to tell their story together, with their children seated beside them. They talked about the birth and death of their daughter, shared pictures of her in the hospital, and then went on to describe the PGD experience from their own perspective: their need to educate the IVF lab on why they were going through IVF, the travel and time away from home, the difficulty of deciding on more treatment or just giving up. Finally, they spoke of the joy of their disease-free daughter, and how much they enjoyed returning to the PGD centre to show her off. The second family spoke about the laws in Italy and their long struggle with PGD which took them outside Italy for treatment. Mr Ponchiroli movingly told us how HLA matching had finally allowed them to have their much desired second child who could also be a bone marrow donor for their sick son at home.

These patient talks were truly an eye-opening experience for everyone in the room. Indeed, there were many tears shed, and it proved a very important part of the celebration, one that I will never forget. It emphatically reminded all of us of why we do the work we do, and I hope we can find more ways to include patients in our scientific meetings.

Gary Harton

From PCR to array CGH in just 20 years. Most centres, said Santiago Munné, have now moved to the latter.



changed, and nowhere was this more sharply seen than in the personal accounts from two PGD families, the one at risk of transmitting spinal muscular atrophy and the other requiring a 'saviour sibling' for HLA tissue matching. Both accounts were a reminder that PGD is all about an individual couple with their own risks and own distress. The technologies might have changed, but the indications for PGD as an alternative to prenatal testing and termination of pregnancy are the same today as ever.

Also never-changing - and what Mark Hughes described as one of three 'realities' in PGD - is controversy, whether over the specific diseases tested in individual couples or in the feasibility of improving IVF success rates by PGS. Much of the PGD controversy, Hughes argued, was reflected in the public and regulatory confusion between testing for 'traits' and for disease. Designing for traits, he said, was still beyond technology, noting that 'the genotype doesn't predict the phenotype very well'. But in his view even rhesus D blood or the dermatological conditions which have given rise to such controversy in the USA are strictly within the bounds of disease. A woman with anti-D antibodies, he said, may carry risks in pregnancy which PGD can prevent. Similarly, although the clinical manifestation might be many years after delivery, PGD is able to screen for the BRCA1 and 2 genes associated with breast cancer and thereby remove that particular risk. So far, said Hughes, 42 babies have been born at his own centre in Detroit following PGD for BRCA1 and 2.

And controversy is likely to continue with the affordable availability of high-throughput genotyping by SNP analysis. Already, companies are targeting consumers with a simple test of genetic susceptibility, but what, asked Hughes, will we do with the information? The technology of PGD and gene analysis is no longer the limiting factor, he argued; the limit lies in how far we're prepared to go and in what fields the technology is judged to be useful and ethical.

The other big question which remains unanswered after 20 years is over the safety of PGD. As Alison Lashwood reported, there is still little long-term follow-up of PGD babies and no strong data to confirm the safety of the technique. The database of the PGD Consortium reflects an overall malformation rate of 3.9%, a rate no higher than abnormality rates in other ART procedures.

The next 20 years will surely answer that outstanding question, but, according to Mark Hughes, PGD will still be analysing a single gene in a single cell, and still trying to deliver a healthy unaffected baby.❑

Speakers with something to celebrate. Back row, from left to right, Santiago Munné, Francesco Florentino, Alan Handyside, Darren Griffin, Dagan Wells, Luca Gianaroli, Joe Leigh Simpson, Anver Kuliev, Guido de Wert, Joep Geraedts, Stéphane Viville; front row, Karen Sermon, Inge Liebaers, Alison Lashwood, Montse Boada, Anna Veiga, Cristina Magli, Leeanda Wilton, Marilyn Monk, Joyce Harper and Mark Hughes. (Pictures: Tommaso Gianaroli)

4.3 million babies born since Louise Brown

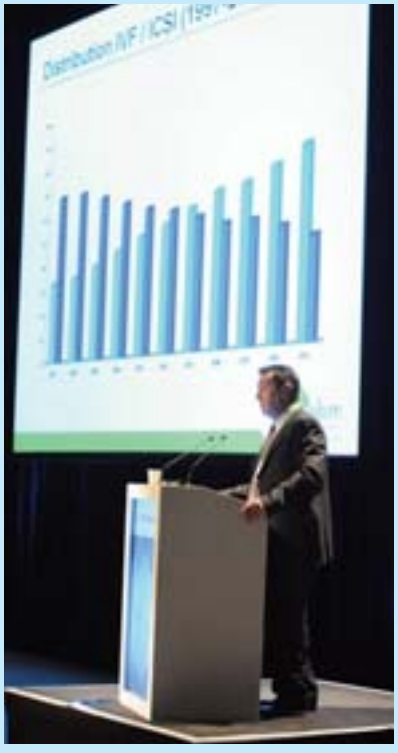
Europe continues to lead the world - and by a long way - in the number of ART treatments performed each year. Jacques de Mouzon, the new chairman of ESHRE's European IVF Monitoring (EIM) group, said that 479,288 IVF and ICSI cycles had been reported from 32 European countries in 2007, almost four times as many as in the USA. The European figures are estimated to represent some 110,000 babies born, the majority conceived by ICSI (67% of all fresh treatments).

However, despite the predominance of 'Europe', De Mouzon stressed 'that data should be looked at from individual countries and compared between countries', rather than as a single European unit. There's little harmonisation in this sector of European activity.

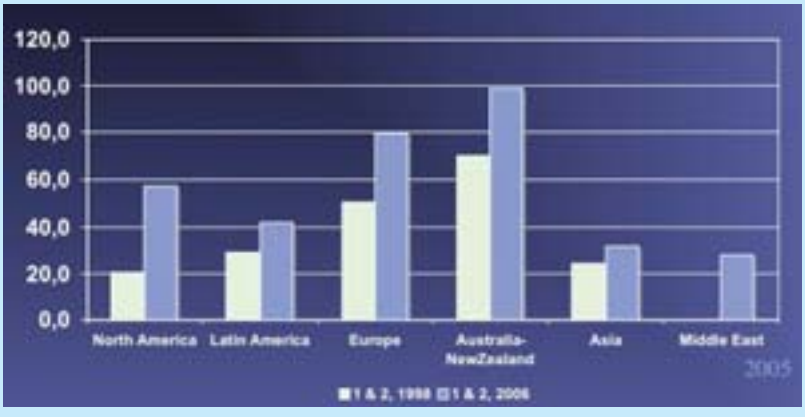
Among those European countries the greatest number of cycles in 2007 were performed in France (66,706), Germany (62,322), Spain (54,620), UK (46,688) and Italy (43,708).

Denmark continues to lead in availability with 2558 cycles per million population in 2007, followed closely by Belgium (2479 cycles per million), both countries having generous reimbursement policies at the time. Among those with fewer than 1000 cycles per million are Germany, Portugal and UK. In Denmark 5% of all babies born were conceived by ART in 2007.

However, despite limited availability, particularly in the more populous countries of Europe, pregnancy rates continue their gradual rise. Indeed, said De Mouzon, the 11-year course of EIM data has seen a steady increase from 26 to 33% pregnancy rate per transfer for IVF and ICSI, from 15 to 22% for frozen transfers and from 27 to 46% for oocyte donation, 'and all this despite the transfer of fewer and fewer embryos'.



Jacques de Mouzon, the new chairman of ESHRE's EIM consortium, reports European results for 2007 in Rome. Below, data from the preliminary world report showing transfers of one or two embryos per region (%) 1998-2006, with Australia now reaching a level of 100%.



Over the same period multiple birth rates declined from 30 to 21%, with a four-fold reduction in triplets from 3.7 to 0.8%. Twin deliveries in 2007 were similar to 2006, at 20.5%.

A preliminary report on world data for 2006, presented by Karl Nygren, a former chairman of the EIM, estimated current global ART activity at 1.5 million cycles per year, an extrapolation from the 856,672 cycles referred to ICMART. That corresponds to around 300,000 babies born each year, and a cumulative total of 4.3 million since Louise Brown in 1978. Mean delivery rate per aspiration in 2006 was 22.1%, but, said Nygren, with huge differences in availability, practice and results.

As in Europe, the global trend is towards a greater use of ICSI over IVF. In 2006 ICSI use increased by 2.5% over the previous year, to account for 65.5% of all world cycles. In the Middle East virtually every cycle is ICSI.

Almost two-thirds of world ART activity is now performed in seven countries, with the most in Japan (139,463 cycles reported) and USA (124,271 cycles), followed by France, Germany, Spain, Australia and UK.

With multiple pregnancy rates ranging between 32 and 12%, the proportion of one and two-embryo transfers also varied greatly throughout the world in 2006 - from 100% in Australia and New Zealand to just 30% in Asia and the Middle East.❑

New members elected to Paramedical Board

Collaboration best describes the activities of the paramedical group so far this year. A Campus training workshop in May on the management of infertility for junior doctors, paramedics and embryologists was organised with the SIGs Reproductive Endocrinology and Embryology, a first collaboration for the PMG - and in a special location of Kiev, Ukraine. Both days of the two-day course were fully booked and all lectures simultaneously translated into Ukrainian. Although English was not the first - or second - language of many delegates, the discussion and comments were interesting and informative. As we say in the Netherlands, it is always an education to look into someone else's kitchen. The collaboration proved so successful that we are now thinking of running the course in another country. We will keep you posted.

Cross-border reproductive care: information and reflection

The PMG's precongress course in Rome was another collaboration, this time with the SIG Ethics & Law on cross-border care. Again, the course was fully booked, with a varied audience which contributed different points of view. Even at the end of the day discussions were so lively that many simply wanted to carry on, reflecting the interest of paramedics in the ethical and legal issues raised by cross-border care.

A training manual for paramedics

For the past two years the PMG has been working on the translation of a Dutch training manual for paramedics. The final version was ready in Rome and we were very proud to present it to our members, 140 of whom collected their copies on site. ESHRE's Central Office will send all other PMG members (more than 400) their free copy later this year.

Membership

Yet again the number of paramedical members has increased - from 9.8% of total ESHRE membership last year to 10.4% this. The majority of PMG members come from Belgium and the Netherlands, and in the coming year we hope to increase the number of members from other countries. To do so we have organised two basic training courses for paramedics new to reproduction who wish to improve their basic knowledge of the underlying causes, treatments and psychological aspects of infertility. The first course will be in Valencia, Spain (7-8th October 2010) and the second in Berlin, Germany (3-4th March 2011).

Changes to the Paramedical Board

In Rome Heidi van Ranst, who has been chairman of the Paramedical Board for the past two years, stepped down and I took over. I am very proud to take on this important job and I hope I will do the same excellent job that Heidi did. With a new chair, there is also a new chair elect, and this will be Helle Bendtsen from Denmark and I want to wish her good luck with preparing herself for this job.

In Rome we also took on some new board members, with many candidates applying. All candidates were considered in detail and board members had to take two votes before the final choice could be made. The current board members are now Patricia Baetens (B), Helle Bentsen (DK), Eline Dancet (BE), Inge Rose Jorgensen (DK), Helen Kendrew (GB), Raquel Robles (ES), Heidi van Ranst (BE) and Cecilia Westin (SE).

Jolieneke Schoonenberg-Pomper
For the Paramedical Board

Legal ruling by federal court overturns Germany's ban on PGD

Germany's Federal Court of Justice ruled in July that PGD was not in violation of the country's embryo protection law, which until then had carried a prison sentence of up to three years for those using embryos in a way which did not promote their survival. The Leipzig court ruled that, because the ultimate goal of PGD is a healthy pregnancy, such tests do not violate the legislation, which has been in place since 1991. The federal court's ruling upheld an earlier decision by a Berlin state court.

This case involved a Berlin clinic which according to reports had performed PGD between 2005 and 2006 in three couples thought to be at risk of transmitting a genetic defect. Knowing the legal implications, the unnamed doctor turned to the courts for clarity. The court's verdict said that 'the accused, a gynecologist who focuses on fertility treatment, has been acquitted of the allegation of threefold violation of the embryo protection law'.

The court's decision prompted a heated reaction in Germany, with a number of conservative politicians calling for tighter laws to ensure that embryo selection remains illegal. While chancellor Angela Merkel's Christian Democratic Union and sister party the Christian Social Union reacted against the verdict, the Free Democratic Party said the ruling opened the door for PGD in Germany.

Understanding the impact of impact factors

A record result for *MHR*

In academic publishing 'impact factor' is a proxy for journal quality. Controversial though it is, IF is widely used to rank journals within a particular field, and inevitably authors tend to prioritise high-impact journals for publication.

The ISI Web of Knowledge website indexed 7347 science journals according to their 2009 IF. The three ESHRE journals are ranked 230 (*Human Reproduction Update*, with an IF of 7.042), 764 (*Human Reproduction*, IF 3.859) and 1241 (*MHR*, IF 3.005).

This ranking, however, improves massively when the journals are judged within the subject categories they cover. Thus, of the 26 journals in 'Reproductive Biology', *HRU* is top, *HR* is third and *MHR* is seventh. And even within the highly competitive 'Development Biology' category *MHR* is ranked 12th of 35.

For me as editor-in-chief of *MHR* our 2009 IF figure, which was released in June, is particularly gratifying because it signals the renaissance of a thriving basic science journal within the ESHRE stable. Our IF has increased by more than 18% in the past year to 3.005, putting it comfortably ahead of *Reproduction* (IF 2.579) and closing in on its major competitor *Biology of Reproduction* (IF 3.3).

Despite an awareness that 'impact factor is not always a reliable instrument' (as Wikipedia notes!), it is still widely used as a measure of academic quality, and *MHR* editorial policy will unapologetically continue to drive up our IF.

Metrics suggest that we might be heading in the right direction. However, in the quest for excellence we also wish to be judged by service to authors and readership. Speedy and authoritative decision-making (currently less than 28 days from submission to first decision) can also help give *MHR* the edge. The 'New Research Horizons' review series, thematic issues and invited papers on important topical subjects, judicious fast-tracking of outstanding articles, and publishing free access articles through Editor's Choice all have a role to play in establishing *MHR* as a journal of first choice in reproductive science.

Steve Hillier
Editor-in-Chief, MHR

Above, MHR editor Steve Hillier and Human Reproduction editor André Van Steirteghem. Below, HR impact factors 2005-2009, and with competing journals.

HR continues to climb

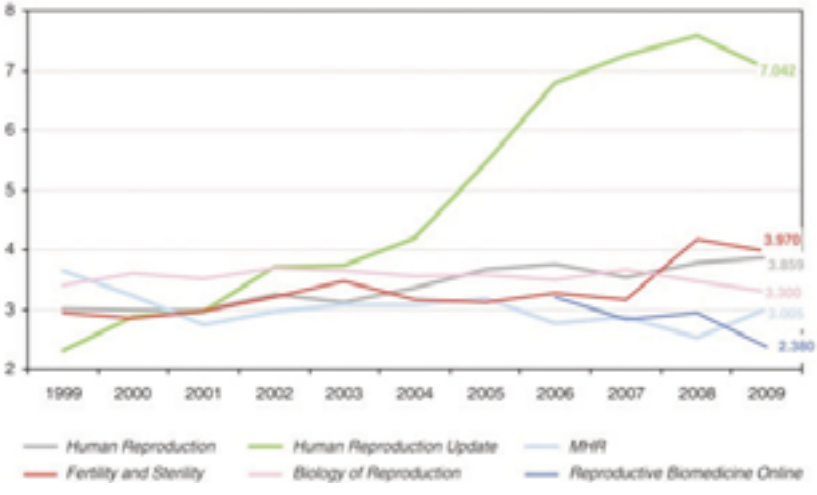
Over the past nine years *Human Reproduction's* IF has increased almost without exception and our categorical ranking has always been in the top four journals. Our IF for 2009, released three weeks before the annual meeting in Rome, is 3.859 and the five-year IF is 3.969.

The Journal Citation Reports, on which the IF is based, deliver statistical information based on citation data, which helps to determine a publication's impact and influence. *HR* features in two subject categories, 'Obstetrics and Gynecology' (70 journals) and 'Reproductive Biology' (26 journals).

The 2009 IF, which continues our steady improvement, represents the average number of times articles published in *HR* in 2007 and 2008 were cited in 2009.

André Van Steirteghem
Editor-in-Chief, Human Reproduction

Year	IF HR	Rank Reproductive Biology	Rank O&G
2005	3.669	3/24	2/52
2006	3.769	2/24	4/57
2007	3.543	3/25	4/60
2008	3.773	3/35	4/61
2009	3.859	3/26	4/70



Next, a third consensus meeting on PCOS

Officers
Adam Balen (GB), Co-ordinator
Richard Anderson (GB), Deputy Co-ordinator
Juan Garcia-Velasco (ES), Deputy Co-ordinator
Georg Griesinger (DE), Junior Deputy
Nick Macklon (NL), Past Co-ordinator

The AGM of the SIG RE was held in Rome on Tuesday 29th June and attended by 20 members of the SIG plus co-ordinators. The minutes of last year's AGM plus the agenda had been circulated to the membership three weeks earlier. We first discussed our recent activities, some of which have already been described in *Focus on Reproduction*. The Campus workshop in Budapest in December, 2009 - 'Old and new hormones' - was a highly successful meeting and covered extremely stimulating topics. The audience was large but mostly local and we agreed in Rome that this should be repeated in another location in the next year or two.

In May we co-ordinated a tripartite meeting between SIGs Endocrinology and Embryology and the Paramedical Group in Kiev. This was planned as a training workshop on the management of infertility for junior doctors, nurses and embryologists. Again, this was a very well attended event, particularly as it took place just before the Ukrainian Fertility Society annual meeting. However, many participants were very experienced and perhaps some of the lectures too basic for them. When we do this again (probably in St Petersburg, on 7-8th September 2011) we may make parallel sessions for those in training and those seeking an advanced update.

The precongress course in Rome on 'The lost ART of OI' had a very high attendance and received much positive feedback. The topics ranged from basic endocrinology to the advanced practice of ovulation induction. The nature of the questions and discussions reinforced the need for practical, clinically based courses.

We were also responsible for the debate in the scientific programme, 'This house believes that multiple natural cycle IVF is preferable to a single stimulated cycle and freezing'. Nick Macklon and Human Fatemi entered into the true spirit of the debate, which was greatly enjoyed by the audience. Once again reproductive endocrinology attracted the highest number of abstracts and the largest number of sessions in the meeting, which made it difficult to chose which direction to run in order to fit everything in.

Former SIG RE co-ordinator Nick Macklon defending the motion in Rome in favour of natural cycle IVF.

Future events

We are involved a number of forthcoming meetings. From 24-25th September we will be in Dubrovnic, Croatia, for 'A healthy start - The determinants of a successful pregnancy'. This is a joint Campus meeting organised with the SIGs Early Pregnancy and Reproductive Surgery. This uniquely designed Campus workshop will bring together those with a special interest in the medical and surgical interventions required to achieve a successful pregnancy outcome. Full details of the programme can be found on the ESHRE website.

The third joint ESHRE/ASRM PCOS consensus meeting on 'Medical Problems associated with PCOS' will be held in Amsterdam from 18-20th November and hosted by Bart Fauser and Basil Tarlatsis. This will begin with a one-day open meeting on all aspects of PCOS (other than those related to fertility) and will proceed to a two-day, closed consensus workshop along the lines of the earlier Rotterdam and Thessaloniki consensus meetings. The open meeting will present the earlier consensus statements and then cover early reproductive life (adolescence, quality of life, obesity, pregnancy) followed by later reproductive life (type 2 diabetes, cardiovascular health and menopause). These consensus meetings have gained significant prominence and the open meeting is likely to be very popular - so please book your place early.

We then go to Madrid (3-4th December 2010) for 'GnRH agonist for triggering of final oocyte maturation-time for a paradigm shift', hosted by Juan Garcia Velasco and Peter Humaidan. This highly topical course will focus on the physiological basis for GnRH agonist triggering to induce final oocyte maturation and the clinical applications of this approach.

We start 2011 in Kempton, Bavaria, on the 4th February, for 'ART and oncological impact', hosted by Ricardo Felberbaum. Topics to be included in this important workshop will cover issues relating to sex

// REPRODUCTIVE GENETICS //

Collaborations reflect the place of genetics in reproduction

Officers
Stéphane Viville (F), Co-ordinator
Sjoerd Repping (NL), Deputy Co-ordinator
Filipa Carvalho (P), Deputy Co-ordinator
Claudia Spits (BE), Junior Deputy
Karen Sermon (BE) Past Co-ordinator

Several of our latest events have been organised in collaboration with other SIGs or Task Forces, and our precongress course in Rome - 'From gametes to embryo: Genetics and developmental biology' - was co-organised with the SIG Embryology. We had a very big audience and, despite the absence of two invited speakers who were replaced at the last minute, it all went very well. This co-organisation of activities underlines the special position of our SIG at the junction of many different specialities.

This year we have already been involved in an ESHRE Campus on 'Approaching accreditation of a PGD centre' in collaboration with EuroGentest in London, the fifth ESHRE Campus on 'Basic Genetics for ART practitioners' in Porto, Portugal, and the ESHRE post-congress course on 20 years of PGD; the activities of the PGD Consortium are closely linked to the SIG-RG.

We expect 2011 to be as busy as this year, with similar activities planned in collaboration with other SIGs or alone. In collaboration we have set up a pecongress course with the SIG Early Pregnancy for Stockholm ('From genes to gestation') and, with the SIG Ethics & Law, a Campus meeting, probably in May 2011, on 'Developments in PGD-PGS and early prenatal testing: scientific dynamics and ethical implications'. We intend to update the latest technological developments and review the debate on current ethical points.

More specifically, we are continuing our ESHRE Campus course 'Basic genetics for ART practitioners' next year in Bucharest. This will be the sixth edition, now encouraged by the high success of the last one and the request from ESHRE to promote activities in Eastern Europe. And in response to further demand, in Stockholm we will also be picking up a post-congress workshop first organised in Lyon in 2008 on 'Biopsy of human eggs and embryos - Troubleshooting'; this will take place immediately after the annual meeting.

Finally, our business meeting in Rome also acknowledged an urgent need for an ESHRE event on embryo epigenetics and on the biology of retrotransposons and their consequences on gametogenesis and fertility.

Stéphane Viville
Co-ordinator SIG Reproductive Genetics

steroids and their oncogenic potency, cancer incidence in infertile women after COH, the incidence of malignancies in children born after IVF, and ovarian protection during chemotherapy by GnRH agonists.

Nick Macklon will be hosting 'The embryo as patient' on 13-14th May in Southampton, UK. It is now clear that the periconceptional period determines not only perinatal outcomes but has an impact on the long-term health of mother and child. The aim of this course is to provide those working within this periconceptional window, such as reproductive endocrinologists and embryologists, a state-of-the-art overview of how fertility interventions during this time affect the long-term health outcomes, and identify strategies for optimising these outcomes in their two patients, the embryo and the mother.

Stockholm 2011

Our precongress course in Stockholm will be on ovarian ageing. The course will cover the formation of oocytes in the ovary and determinants of their rate of loss. Detailed descriptions will be given of factors influencing oocyte quality and thereby potential fertility and how these may be quantified. The causes and management of premature ovarian failure will be described, as will ways to preserve fertility by either oocyte or ovarian tissue cryopreservation. We will conclude with a socio-ethical talk on the effect on society of postponing pregnancy, access to infertility treatment and its financial implications.

We have discussed a number of suggestions for topics for future meetings, which will be circulated by e-mail. These include puberty/adolescent gynaecology, GnRH antagonists, AMH, adjunctive therapies for ART (aspirin, DHEA, growth hormone, steroids, heparin, acupuncture, homeopathy . . .), lifestyle and reproductive dysfunction, and IVF regimens. These are all attractive suggestions, and if you have further ideas or comment - in particular which topic you might prefer in Istanbul - please contact me.

I stand down as co-ordinator in 2011 and Georg Griesinger was proposed and elected to take over after Stockholm. Two new members of the SIG will be required to supersede Richard Anderson and Juan Garcia-Velasco as deputy co-ordinators. If you would like to be considered, again please contact me so we can hold a vote.

Adam Balen
Co-ordinator SIG Reproductive Endocrinology
adam.balen@leedsth.nhs.uk.

SPECIAL INTEREST GROUPS

// REPRODUCTIVE SURGERY //

A widespread future for our new techniques?

Officers
Marco Gergolet (IT), Co-ordinator
Vasilios Tanos (CY), Deputy Co-ordinator
Rudi Campo (BE), Deputy Co-ordinator
Pietro Gambadauro (IT), Junior Deputy
Stephan Gordts (BE), Past Co-ordinator

How much is too much, someone asked at our precongress course on NOTES and single access surgery. Indeed, the surgery presented by several of our speakers seemed at the limit, verging on the 'impossible'. But the same words were said 20 or 25 years ago about laparoscopic surgery. Then, expert surgeons and academic teachers were sceptical about simple laparoscopic ovarian cyst ablation, not to mention myomectomy or hysterectomy. But over the following years an improvement in surgical skill and the development of new tools allowed us to perform routinely procedures considered at the limit a few years before.

The techniques of NOTES (Natural Orifice Transluminal Endoscopic Surgery) and single access surgery are overlapping, but are not the same. In NOTES access is intra luminal (transgastric, transesophageal, or transvaginal) whereas single access surgery is mostly transumbilical. Some authors consider the umbilicus an embryological lumen, and define single access surgery as embryological NOTES (eNOTES) or NOTUS (Natural Orifice TransUmbilical Surgery).

The live surgery session attracted a big audience in Rome.

The techniques are so new that there is even a lack of uniformity in the definition. The same procedure may be called SITRACC (Single Trocar Access), SAS (Single Access Surgery) and so on. According to the speakers, Marcus Dantas from Rio de Janeiro and Silvana Peretta and Joseph Nassif from IRCAD, Strasbourg, it is not yet clear if the techniques have a widespread future. However, manufacturers have already developed new (articulated) instruments, which may be useful soon in traditional laparoscopy. In conclusion, if only 10% of the presented techniques find a wide clinical application, this will still be a huge step in the future of endoscopic surgery.

At our business meeting in Rome, the SIG RS board began its last year of duty. Following nominations and elections, Vasilios Tanos from Cyprus will become the new Co-ordinator in Stockholm. The proposed and elected deputies were TC Li (GB) and Grigoris Grimbizis (Greece) and Natasa Kenda-Suster (SI) as Junior Deputy.

Marco Gergolet
Co-ordinator
SIG Reproductive Surgery

// SAFETY & QUALITY IN ART //

A patient-centred approach to remain the focus of attention

Officers
Petra De Sutter (BE), Co-ordinator
Karl Nygren (SE), Deputy Co-ordinator
Wiliane Nelen (NL) , Deputy Co-ordinator
Jan Kremer (NL), Past Co-ordinator

The SIG Safety & Quality in ART (SQART) contributed to a well attended precongress course on 'Patient-centered fertility care' in Rome. This topic will remain the focus of our activities in the coming year, with a patient-focused approach becoming more and more important in infertility treatment today. Our precongress course now in planning for next year's annual meeting in Stockholm will continue to develop this subject.

At the business meeting of SQART in Rome we determined to concentrate on the vision and mission of the SIG and, since safety and quality are fundamental to all areas of ART, be it embryology, endocrinology or early pregnancy, we will try to develop themes which embrace all these domains and are of likely interest to other SIGS in the future. We are open to ideas, so please feel free to contact any of us with any you might have. Meanwhile, we will keep you posted on future activities of the SIG SQART.

Petra De Sutter
Co-ordinator SIG SQART

A 'very productive and successful year'

Officers
Cristina Magli (IT), Co-ordinator
Maria José de los Santos (ES), Deputy Co-ordinator
Kersti Lundin (SE), Deputy Co-ordinator
Josephine Lemmen (DK), Junior Deputy
Etienne Van den Abbeel (BE), Past Co-ordinator

SIG Embryology activities in Rome began with our precongress course held jointly with the SIG Reproductive Genetics reviewing the events regulating gametogenesis and embryogenesis both in vivo and vitro. Altogether, this was an excellent educational day that attracted 300 participants keen to enhance their knowledge of embryo formation.

As in previous years, the embryology sessions in the main programme were extremely interesting and well attended, with lively discussions. Of special relevance was the debate on 'Selection of male/female gametes: which is more informative?' Laura Rienzi and Chris Barrat provided the scientific evidence but in such a brilliant way that the audience was totally engaged by their performance.

No doubting who won the debate on the selection of male or female gametes - even if not quite by a knock-out. Laura Rienzi salutes her home crowd in Rome.

The Poster Village provided an opportunity for the second consecutive year of presenting paper and electronic posters. It seems a successful initiative, with more poster boards than in Amsterdam. During the time assigned to discussion of the embryology posters, many constructive comments were raised, highlighting how interaction provides a strong advantage over electronic posters.

One-year activities

Since Amsterdam 2009 we have hosted courses in Athens ('Cryobiology and cryopreservation of human gametes and embryos'), Potsdam ('6th workshop on mammalian folliculogenesis and oogenesis', organised in collaboration with the Task Force Basic Reproductive Science and SIG Reproductive Genetics), Maribor ('The search for excellence in IVF: a practical approach'), Bologna ('Poor ovarian response' in collaboration with all ESHRE SIGs), and Kiev ('The management of infertility - Training workshop for juniors, paramedics and embryologists' as a joint activity with the SIG Reproductive Endocrinology and Paramedical Group).

At the request of the PGD Consortium we have developed the text for the new embryo biopsy guidelines now awaiting publication, and have also organised the working groups for the new *Atlas of Embryology* which, under the co-ordination of Gayle Jones, are already active.

Forthcoming activities

The next SIG Embryology meeting will be in Lisbon on 9-10th October on 'Forgotten knowledge about gamete physiology and its impact on embryo quality'. Here, we'll revisit concepts on the cell biology of gametogenesis, fertilisation and early embryo development, to provide an overview of the mechanisms regulating cell growth.

The SIG Embryology will stage a one-day postgraduate course at this year's ASRM meeting in Denver on 'The enrichment of culture media: towards the best environment for IVF embryos?'. Speakers have prepared an excellent programme illustrating how, in the enrichment of media, several growth factors, antioxidants and vitamins are added at concentrations which, quite often, are far from physiological. Concerns have been raised on this approach and there is a need to understand whether promoting embryo growth so aggressively might have an effect on later development.

Next year in Salzburg, 1-2nd April, we are running a Campus course on 'Practical aspects of non-invasive selection of gametes, embryos and blastocysts in a modern IVF laboratory'. The programme is already finalised and aims to give an update on selection processes throughout preimplantation development. The course will assist clinical embryologists select gametes, embryos and blastocysts with the highest viability, not only on the basis of light-microscopical evaluation, but also according to more advanced and newer technologies. This course - like our event in Lisbon - is organised in collaboration with the local reproductive medicine society.

Finally, our precongress course for Stockholm in 2011, 'The blastocyst: perpetuating life', will be held jointly with the SIG Stem Cells. Although the topics mainly consider basic scientific findings, each of them has potential implications for IVF or regenerative medicine.

Thus, we consider this to have been a very productive and successful year for the SIG Embryology, partly because of our close interaction with other SIGs and Task Forces and with the national societies, with whom we are trying to establish a common line of action. It is a big organisational effort, but we firmly believe our members deserve it.

Cristina Magli
Co-ordinator SIG Embryology

An exchange scheme for 'young' members

Officers
Hilary Critchley (GB), Co-ordinator
Anneli Stavreus-Evers (SE), Deputy Co-ordinator Endometrium
Gerard Dunselman (NL), Deputy Co-ordinator Endometriosis
Annemiek Nap (NL), Junior Deputy
Thomas D'Hooghe (BE), Past Co-ordinator

The SIGEE enjoyed a high profile in Rome, with abstracts in endometriosis, endometrium and implantation well presented in oral and poster communication. Our pre-congress course focusing on how new technologies may be applied in the context of endometriosis attracted a full house, and we owe thanks to Juan Garcia-Velasco and Paola Vigano for putting together such a superb programme; the course has certainly set a standard for those to follow.

In this context our precongress course in Stockholm has kept a lower profile in endometriosis so as not to compete with the World Congress some few weeks later in Montpellier (4-7th September 2011). Nevertheless, our 2011 precongress course has an attractive agenda focusing on the impact of the reproductive environment on implantation success. The course will address both systemic and local environmental influences on embryo implantation and should appeal to all obstetricians, gynaecologists and practitioners with an interest in managing patients in early pregnancy or with problematic early pregnancy - particularly those patients who may also suffer with endometriosis or fibroids.

Future Campus events

The SIGEE is involved in a tripartite Campus with the SIGs Early Pregnancy and Stem Cells on the maternal-embryonic interface. This will be held in Valencia 2-3rd December over one and a half days. More details are on the Calendar pages of the ESHRE website. Importantly, this event has provided an opportunity for presentations from nine junior SIG members, and we hope to encourage other juniors (clinical and non-clinical) to submit their work and join us in Valencia. The abstract deadline is 4th November 2010

More specifically we will be staging a Campus course on 'IVF and endometriosis' in Rome in May 2011. Certainly, the treatment of endometriosis-associated infertility can benefit from guideline recommendations but this remains a dynamic topic. The objective of the course will be to present and discuss emerging ideas in the context of recognised treatment approaches and to provide an update view on optimal care.

SIGEE Junior activities

Our Junior faculty has been extremely active over the past few months working on two topics: improvement of the SIGEE website, and initiating an exchange programme for young clinicians and investigators. One of the new sections for the website is 'High quality publications'. If you have written or read an article which may be a future classic just e-mail our junior co-ordinator at anap@alysis.nl.

We are also working on an exchange programme to stimulate international contacts among those working with patients with endometriosis or endometrium related problems, and improve patient care by learning from each other. The most important goals for young investigators are to improve co-operation in research. 'Young' incidentally refers more to experience than to age. Currently, we are working on a list of candidate exchange centres; criteria for participation in the programme are a referral centre for endometriosis, availability of training/teaching; availability of ART, multidisciplinary endometriosis team, and regular endometriosis surgery including laparoscopy. If you are interested in participating as a young clinician or investigator - or as an exchange centre - please contact our junior co-ordinator Andrew Horne (andrew.horne@ed.ac.uk).

World Endometriosis Research Foundation (WERF)

WERF has made progress in all its three studies this year.

- The Global Study of Womens Health involving 16 centres in ten countries recruited 1418 women to investigate the impact of endometriosis. Preliminary results were announced in Rome during one of the endometriosis sessions and are available at (http://www.endometriosisfoundation.org/press_gswh_june10.php). The full paper will be submitted for publication this autumn.
- The Women's Health Symptoms Study involving 19 centres in 13 countries has investigated the predictability of endometriosis. The study team is knee-deep in data and hopes to submit for publication in September.
- EndoCost involving 12 centres in ten countries has recruited 900 women and also hopes to submit their first, of several papers in September/October.

Politics

Diana Wallis MEP stood up in the European Parliament on International Womens Day and used her one minute to talk about endometriosis - the video can be seen at http://www.youtube.com/user/aldeadle#p/u/81/2sMkvn_wqyo

Hilary Critchley
Co-ordinator SIG Endometriosis & Endometrium

Growing interest in early pregnancy topics

Officers
Ole Christiansen (DK), Co-ordinator
Mariette Goddijn (NL), Deputy Co-ordinator
Siobhan Quenby (GB), Deputy Co-ordinator
Marcin Rajewski (PL), Junior Deputy
Roy Farquharson (GB), Past Co-ordinator

Our precongress course in Rome was a success dominated by two very timely and relevant debates: one between Lesley Regan and Carl Laskin on the use of heparin and low dose aspirin in the treatment of recurrent miscarriage. Both debaters argued convincingly (Regan in favour, Laskin against) but it became clear that the evidence for anticoagulation therapy in patients without high titres of cardiolipin antibodies or the lupus anticoagulant is weak. The recent publication of a series of large randomised trials has shaken belief that these initially promising treatments will be helpful in such patients.

The other debate, between Mary Stephenson and our Junior Deputy Mariette Godijn, highlighted the diversity of views across the Atlantic in how to detect in the most cost-efficient way parental chromosomal translocations in couples with recurrent miscarriage. One strategy is to restrict parental karyotyping to couples with a miscarried embryo with a documented unbalanced karyotype; another is to do selective parental karyotyping in high-risk patients.

Another presentation which caused much discussion was by Henriette Nielsen who suggested from her own studies that immunity against male-specific antigens plays an important role in secondary recurrent miscarriage.

At the SIG-EP's business meeting in Rome Ole B. Christiansen took over as the new SIG Co-ordinator from Roy Farquharson. Everyone agreed that Roy has done a tremendous job in the organisation of meetings and in increasing interest in early pregnancy topics in ESHRE.

There were three early pregnancy sessions in the main programme of which one - on the Monday afternoon - attracted a huge (~2000) audience. Results from several large placebo-controlled trials of treatment for recurrent miscarriage were presented, as well as from a large Scottish epidemiological study suggesting that a short time interval from miscarriage to next pregnancy may decrease the risk of a new miscarriage and other complications - in contrast to WHO guidelines.

Future activities

Our next activity will be a joint Campus with the SIGs Reproductive Surgery and Reproductive Endocrinology in beautiful Dubrovnik on 24-25th September. Titled 'The determinants of a successful pregnancy', obesity and advanced maternal age will be key topics.

On 2-3rd December we are hosting a joint meeting in Valencia with the SIGs Stem Cells and Endometriosis/ Endometrium on 'The maternal embryonic interface'.

Our precongress course in Stockholm will be a joint course with the SIG Reproductive Genetics, with focus on the genetic aspects of fertilisation, ART, implantation and early pregnancy.

Ole B. Christiansen
Co-ordinator SIG Early Pregnancy
olbc@rn.dk

Options for new guideline and position papers under discussion

Sheena Lewis will succeed Roelof Menkveld as SIG Andrology Co-ordinator at next year's annual meeting in Stockholm. Sheena is Professor of Reproductive Medicine at Queen's University in Belfast.

Our precongress event in Rome was a 'Basic course on the environment and human male reproduction', a scientifically orientated meeting, which proved popular. Next year our precongress course will be on 'Lifestyle and male reproduction', this time a more clinically orientated meeting.

The annual meeting for participants in the semen analyses external quality assessment (EQA) scheme run under the banner of SIG-A was also well attended, and several options for guidelines and position papers were discussed.

Near future activities include a basic semen analysis course in Barcelona from 20-23rd September this year and a combined Campus meeting with the SIG Reproductive Surgery on surgery in female and male infertility patients, which will take part in Treviso, Italy on 8-9th October. We are also, under the guidance of Sheena, busy planning several combined Campus meetings for 2011.

Roelof Menkveld
Co-ordinator SIG-AndrologY, rme@sun.ac.z

The Catholic perspective on ART: a 'missed opportunity' in Rome to reflect its relevance

This year, ESHRE's Historical Lecture - appropriately in Rome on Catholicism and human reproduction - was given by Dr Norman Ford, and it was no surprise, at a meeting in the shadow of the Vatican, that an expert in Catholic ethics should be invited for this prestigious address. Moreover, Dr Ford has written a famous book, *When did I begin? Conception of the human individual in history, philosophy and science* (Cambridge, 1998), which reflected his ability to integrate the findings of life sciences with ethical thinking.

His lecture addressed three (clusters of) issues:

1. The status of the embryo. Dr Ford agreed with theological and papal statements that in the light of contemporary embryology it is reasonable to hold that the fertilised egg is a living human individual, and even a human person. This was a surprise to many of us, because in his book he had actually argued that the human individual could not begin before definite individuation occurs with the appearance of the primitive streak some two weeks after fertilisation.

2. The link between procreation and 'the conjugal act'. The Roman Catholic Church teaches that it is ethically unacceptable to dissociate the two - so, even if IVF did not destroy human embryos (embryonic persons), it would still be at odds with this doctrine. Dr Ford added a consequentialist argument, namely that such dissociation does not serve the long-term interests of children thus conceived.

3. Ethics and ART. Dr Ford briefly focused on the ethics of certain selected technologies. Sex selection, so he stated, is legitimately employed for the breeding of animals, but in human reproduction it is discriminatory and at odds with the dignity of children.

The lecture was felt by many to be disappointing. I personally had expected a more open and critical reflection (as in *When did I begin?*). What matters in ethics is not the argument of the authority, but the authority of the argument. When I asked Dr Ford why he had changed his view on the status of the embryo, he simply replied that people are free to change their minds (which is obviously true), and that we have the responsibility to search for the truth - begging the question as to why what he now considers as 'true' had earlier been rejected 'false'.

His lecture (in fact, no more than a series of apodictic statements) raised many other questions. For example, why is the link between procreation and sex crucial? What's wrong when people who are unable to conceive naturally use technology to fulfil their wish for a child? Is there any evidence that medically assisted reproduction is by definition at odds with the interests of children thus conceived? Is sex selection necessarily discriminatory? Wouldn't it make sense to make a distinction between medical and non-medical motives and, with regard to the latter, between motives that are clearly discriminatory and motives that probably are not?

I am afraid that even from the perspective of those sympathetic to the Roman Catholic Church, the lecture was a missed opportunity to show that Catholic moral thinking need not be dogmatic and to convince the audience that its teachings are still relevant for medically assisted reproduction.

Guido de Wert
Professor of Biomedical Ethics, Maastricht University
Co-ordinator TF Ethics & Law

The UK's HFEA to be scrapped in money-saving purge

The UK's Human Fertilisation and Embryology Authority, set up in 1991 to license and monitor clinics performing ART and human embryo research and to regulate the storage of gametes and embryos, is to be axed in a round of cost-cutting moves announced in July by the UK's new coalition government.

The HFEA will continue to function for a while, but will transfer its legal duties within the next four or five years (the duration of the present Parliament) to a new research regulator and the Care Quality Commission.

The HFEA was established as part of the 1990 Human Fertilisation and Embryology Act and, as a function of its statutory remit, required licensed clinics to submit data on every treatment cycle performed. While the immediate consequence was controversial - annual league tables of clinic performance - the longer term provided a cumulative database of ART practice which few countries in the world can match. Some of the past's landmark studies - such as Templeton's 1998 report on reducing multiple pregnancy by transferring two embryos - were based on the HFEA database.

In Stockholm next year the HFEA will be involved in an invited session on single embryo transfer, with presentation of results from the database.❑

ESHRE in new collaboration to improve availability and quality of fertility treatments in HIV-positive couples

AUGUSTO SEMPRINI: 'THE MAJORITY OF THOSE INFECTED BY AIDS ARE OF CHILDBEARING AGE AND THEIR DESIRE FOR PARENTHOOD IS PSYCHOLOGICALLY AND BIOLOGICALLY SOUND.'

A Task Force for Fertility and Viral Diseases is one of three new ESHRE Task Forces introduced in Rome. Its aim is to develop a collaboration between ESHRE and the Centres for Reproductive Assistance Techniques in HIV in Europe (CREAThE), a non-profit organisation registered in Italy and committed to improving the quality and availability of safer fertility options for couples affected by HIV and/or other transmissible infections. CREAThE presently comprises 13 active members representing clinical centres from 12 countries.

The Task Force's co-ordinator, Augusto Semprini from Milan, reported that the majority of those infected with HIV are of childbearing age, and their desire for parenthood is psychologically and biologically sound.

However, spontaneous conception attempts inevitably involve the risk of HIV transmission to the uninfected partner and/or the unborn child. Sperm washing is currently the recommended approach for couples trying to conceive when the man is infected with HIV; however for some couples this treatment may be difficult to access.

CREAThE is also collaborating with CONRAD, an independent agency of the CDC in Atlanta, whose overall aim is similarly to improve reproductive health, especially in developing countries and in the prevention of HIV transmission. A large retrospective study on semen washing and IUI has recently been conducted by CREAThE and CONRAD on safe conception for HIV-discordant couples with processed semen from the HIV-infected partner and is now submitted for publication.

A multicentre retrospective study performed by the CREAThE centres and published in 2007 demonstrated that ART following sperm washing significantly reduced the risk of HIV-1 transmission to the uninfected female partner in a total of 580 pregnancies from 3315 ART cycles.[1] All tests were negative. The results, said Semprini, support the view that ART with sperm washing could not be denied to sero-discordant couples in developed countries and, where possible, could be integrated into a global public health initiative against HIV in developing countries.

Today, he explained, more than 15,000 cycles of IUI or IVF with washed semen have been conducted in Europe, without any reported transmission of HIV to the partner woman.

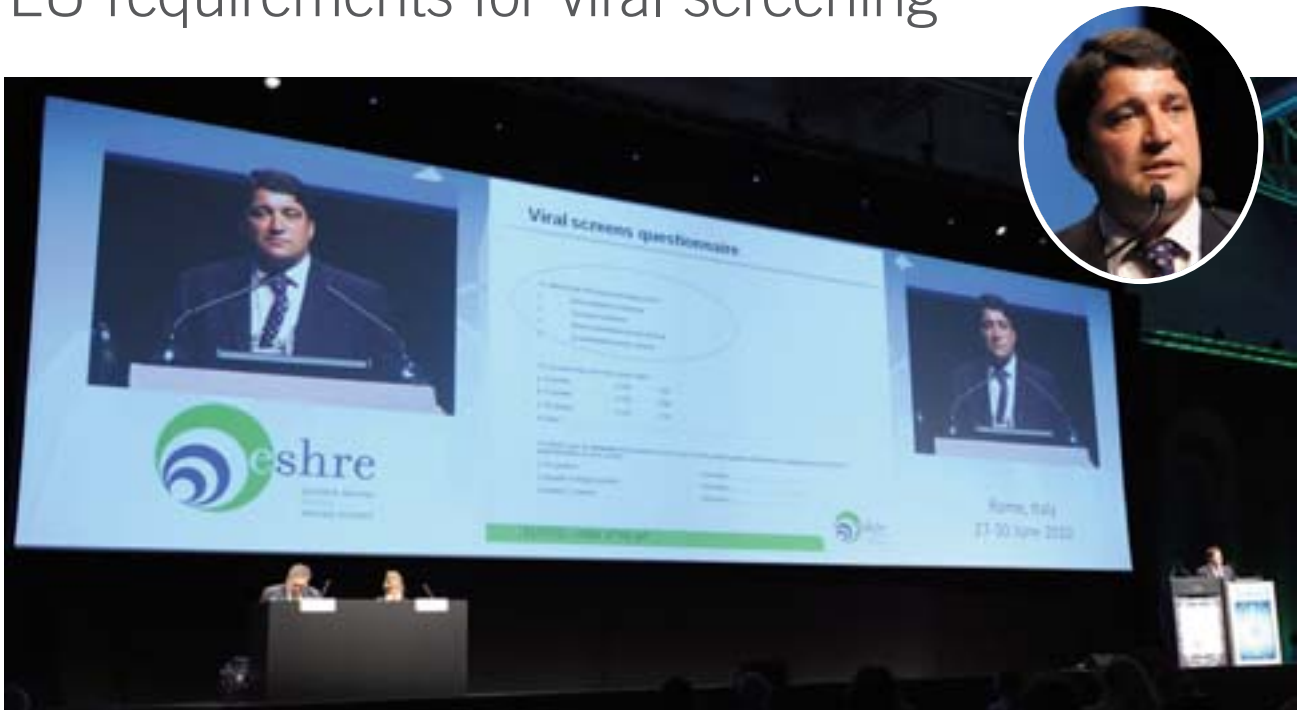
CREAThE's collaboration with ESHRE, said Semprini, aims to investigate the factors involved in the sexual transmission of viruses and their influence on reproductive decision-making and practice, and to understand the influence of viruses in reproduction. In Stockholm the Task Forec will host a precongress course on ART in couples with HIV.

CREAThE is also running a European registry of ART in HIV-positive couples known as SHARE (Studying HIV and Reproduction in Europe) supported by a Zegna Foundation grant. The registry is collecting data from centres which offer reproductive counselling and treatment for inclusion in a database. The project aims to recruit data on 1000 couples.

● More information on the CREAThE organisation can be found at www.creathe.org and at www.eshre.eu.

1. Bujan L, Hollander L, Coudert M, et al. Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network. AIDS 2007; 21: 1909-1914.

Survey finds inconsistent interpretation of EU requirements for viral screening



Results from a Task Force survey reported by Edgar Mocanu in Rome found that 15 of 19 member states surveyed have fully implemented the EUTCD, but interpretations of requirements for viral screening are inconsistent.

A survey conducted by ESHRE's Task Force on the EU Tissues & Cells Directives among 27 member states (without response from Cyprus, Estonia, Germany, Latvia, Lithuania, Malta and Slovakia) has found that, of 19 countries with more than one fertility unit:

- 16/19 have a competent authority in place
- 12/19 the competent authorities have sought consultation from the ART sector
- 15/19 have fully implemented the three directives
- inspections have begun in 12/19 and concluded in 6/12.

Speaking at an ESHRE information session in Rome, the Task Force's co-ordinator, Edgar Mocanu from Dublin, Ireland, thus concluded that the directives have not yet been fully implemented or inspected so far and that 'the time remains ripe' for member states to work together on their full implementation.

Working together, he added, would be especially important over the contentious issue of viral screening in ART, where interpretation of the requirement varies widely among EU countries.

Indeed, the same questionnaire sent out by the Task Force not only found variance in national requirements for serological testing, but even inconsistency in the definition of what a treatment cycle was. Ten of the 19 member states defined 'treatment' as a single oocyte recovery procedure, but one also included subsequent frozen cycles, and two made no definition at all. One in three considered a 'chain' of egg collections as a cycle.

Nevertheless, in all countries patients do require viral screening before treatment (although Ireland seems alone in forcing testing within 30 days of egg collection in every cycle of treatment); eight of the 19 countries require testing every 12 months, while six of them every six months (and two every two years).

When asked to give an estimate of the number of new cases of viral positive patients detected as a consequence of EUTCD implementation, six countries provided best guesses - of 100 cases of hepatitis C per 31,446 cycles per year, 143 cases of hepatitis B, and 25 cases of HIV. Such guesstimates, said Mocanu, fall far short of the predicted estimates of the EUTCD, and certainly appear between two and five times less high than in the general population.

Questions from the floor in Rome expressed surprise - and frustration - that such requirements seemed to have been developed within the sole context of organ and tissue transplantation, and with little reference to the ART sector. ❑

The way to go: global access to fertility care

Infertility is a global problem with a silent population of more than 80 million couples facing the prospect - and consequences - of childlessness every day. But despite this high prevalence and the cultural values associated with children, infertility care remains a low priority area for local healthcare providers and community leaders. It has been marginalised and is now a neglected area of sexual and reproductive health.

Infertility care in most developing countries is fragmented between public and private sectors. It has been reported that inadequate regulations about treatment conditions and commercial interests has led to unethical practices. Limited information is provided to patients about, for example, success rates and side effects. Overall, very little is known about practice and results in Africa.

The Task Force has recognised the importance, when implementing low-cost (accessible) infertility services in poor-resource areas, of studying social, psychological, sexual, legal and ethical aspects of infertility and its treatment and taking study findings into account when setting up gender and culturally sensitive services.

We aim to tackle all factors associated with childlessness in resource-poor countries, and it is important to find out what the real demands are of the local society and the local fertility specialists. To be involved in these activities is an important part of our future.

ESHRE lecture at the GIERAF meeting, Douala, Cameroon

Earlier this year a meeting held in Douala, Cameroon, by GIERAF (Groupe Interafricain d'Etude, de Recherche et d'Application sur la Fertilité) considered the problem of how to organise ART in Francophone Africa. Our Task Force was invited to talk about the Arusha project, with Willem Ombelet (Co-ordinator) describing the project and future activities, with an emphasis on implementation and accessibility of services in developing countries. The meeting proved very interactive and stimulating, and was attended by more than 150 African specialists.

The third congress of GIERAF will take place in Abidjan, Ivory Coast, in February 2011. We agreed that our Task Force will try to organise a precongress training course on intrauterine insemination (clinical and laboratory aspects).

The organising committee of the GIERAF in Cameroon, with the Cameroon Minister of Health third from left.

Social study group

A Social Study Group has been formed, co-ordinated by Frank van Balen, to address socio-cultural, ethical and sexual aspects arising from our Arusha Project. The objectives of the group have now been defined:

- To develop an insight into the social, cultural, religious, ethical and sexual aspects of infertility in developing countries, including pathways to healthcare and access to treatment.
- To publish overviews of these findings and communicate them to those involved in the Arusha Project, and to a wider audience (including patients, medical professionals, press, NGOs and political and governmental institutions).
- To prepare, monitor and assess social, cultural, religious, ethical and sexual aspects relevant for the implementation of low-cost infertility services in developing countries.

In Rome a monograph was distributed summarising the discussions and topics raised at an expert meeting organised by the Study Group in Genk in December last year.

ESHRE lecture at the ISMAAR, Yokohama, Japan

A special session on ESHRE's initiative in developing countries was held in Yokohama at the 3rd World Congress of ISMAAR (International Society for Mils Approaches in Assisted Reproduction). Our three lectures, presented by Willem Ombelet, Ian Cooke and Sudarshan Ghosh-Dastidar raised much interest such that, for the 4th ISMAAR congress in January 2011 in Calcutta the topic of childlessness in developing countries will be raised again, with Indian healthcare politicians already invited to meet representatives of the Task Force.

Willem Ombelet
Co-ordinator TF Developing Countries and Infertility

GENERAL ASSEMBLY OF MEMBERS

// ANNUAL MEETING 2010 //

ESHRE's General Assembly of Members took place at the Nuova Fiera di Roma on 29th June 2010 at 18.00. The minutes of the meeting are recorded below. Matters arising and their approval will take place at next year's Assembly in Stockholm.

1. Minutes of the last meeting held in Amsterdam

- The minutes of the 2009 General Assembly of Members (AGM), having been circulated to all members in *Focus on Reproduction* (September 2009), were approved. There were no matters arising.

2. Future activities of the Society

Annual meetings

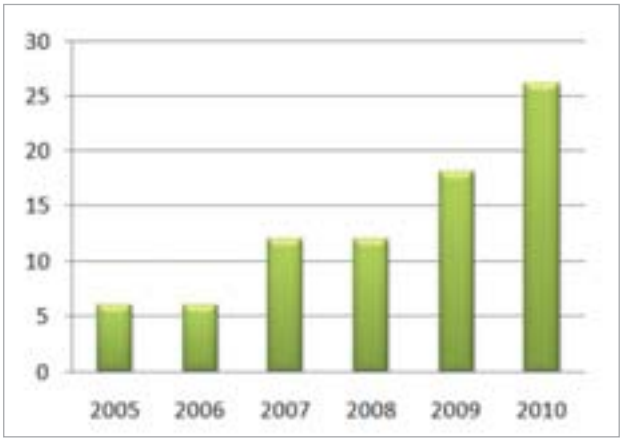
- The Chairman reported that a total of 1539 abstracts had been submitted for the 2010 event, of which 239 (15.5%) had been accepted as oral presentations and 579 as posters. Submissions represented all topic categories, with reproductive endocrinology, andrology and embryology the most popular.
- The Society's 27th annual meeting will take place in Stockholm from 3-6th July 2011 at the Stockholmsmässan. Chair of the conference is Kersti Lundin with Karl Nygren and Outi Hovatta as co-chairs.
- The 28th annual meeting will be held in Istanbul from 1-4th July 2012 at the Istanbul Congress Center. Istanbul, said the Chairman, will be a convenient location for many colleagues and members in the Middle and Far East.

Campus events

- The Society continues to extend its training and update activities with a total of 26 Campus events scheduled for 2010. These include a meeting in Munich in September planned to celebrate ten years of data collection by ESHRE's European IVF Monitoring (EIM) group. The Chairman also noted an increasing number of Campus events jointly organised by several SIGs and Task Forces with overlapping themes.
- Certificates of attendance at Campus events are only available online, and a brief calendar of all events is now printed as an insert to *Focus on Reproduction*.

Task Forces

- The Chairman noted the completion of a proof-of-principle study performed by the PGS Task Force into the accuracy of polar body testing by array CGH for preimplantation genetic screening. The pilot study had met its main endpoints and will now be developed as a randomised clinical trial.
- The former European Assisted Conception Consortium (EACC) has been re-assembled and renamed by ESHRE as the EU Tissues & Cells Directive Task Force under the co-ordination of Dr Edgar Mocanu from Dublin. The TF's first objective is to ascertain the impact and uptake of the EUTCD in Europe and address the contentious question of requirements for viral screening in ART.
- The Task Force Cross-Border Reproductive Care has also been active with publication of its first survey in March and a summit meeting with national authorities in May to discuss development of a Code of Practice.
- A new Task Force for the Management of Fertility Units has been established to help ESHRE members organise their centres and to broaden their management expertise. This new TF presented results of a survey of clinic priorities in Rome which included human resources, financial management and insurance.



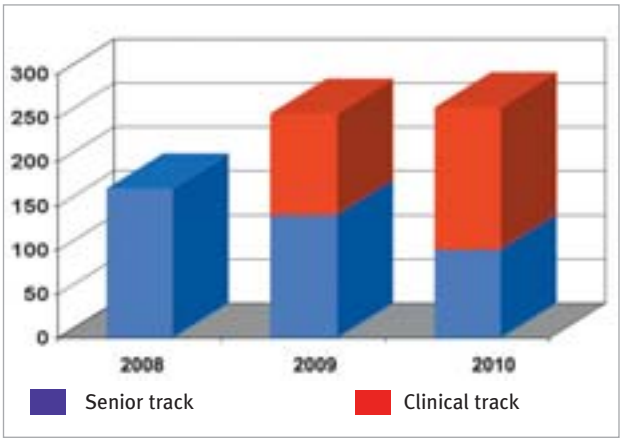
Campus events 2005-2010. With workshops and training a reaffirmed priority, SIG and Task Force expenditure is expected to reach 1,354,375 euro in 2010.

Embryology certification

- Kersti Lundin, chair of the Embryologists' Certification Committee (EmCC), reported that just over 250 sat the certification exam in Rome, with more enrolled this year for the clinical embryology track than for the senior track. Dr Lundin said that the organisational structure of the EmCC had now been formalised, with clarification of board constitution and rotation, its main tasks, and rules for handling complaints. She added that ESHRE certification can now be upgraded as CEE (continuous embryology education) through courses, publications, workshops and online training.
- Kersti Lundin's term as chair of the EmCC came to an end in Rome; she will be replaced by Francesca Vidal from Spain.

Collaborations

- ESHRE will take part as an associate partner in the Substances of Human Origin - Vigilance and Surveillance (SOHOV&S) project as a follow up of the EUSTITE project, co-ordinated by the Italian Transplant Centre (CNT) and funded by the European Commission. ESHRE is the society of reference in ART and provides expertise in several work packages, including the reporting of serious adverse events



Applications for ESHRE embryology certification since the scheme was launched in 2008.

and reactions in ART.
- The Society, through the SIG Reproductive Surgery, will also help organise the Trial of OutPatient Hysteroscopy (TROPHY), a multicentre study designed to assess the effectiveness of office hysteroscopy for improving IVF outcome after repeated IVF failures. The trial will be conducted by the European Academy of Gynecological Surgery with the support of ESHRE.

3. Election of honorary members for 2011

- The two nominees proposed by the Executive Committee for honorary membership in 2011 were Alan Trounson (international) and Lars Hamberger (national). Both nominations were ratified by the AGM.

4. Paramedical Group

- Heidi Van Ranst, Chairman of the PMG board, reported an active meeting for the group in Rome, with a well attended pre-congress course and sessions within the scientific programme. Membership of the PMG stands at 589, 10.4% of the Society's full membership, and continues to grow.
- Heidi previewed two basic training courses in the coming year, one in Valencia, Spain, in October, and the second in Berlin in March. Heidi reaffirmed the importance of the PMG for nurses and technicians in providing a friendly environment for training and reporting their work, and urged clinic directors to encourage membership among their junior colleagues.
- Heidi's two-year term as chair of the Paramedical Board came to an end in Rome; she will be replaced by Jolieneke Schoonenberg-Pomper, a nurse practitioner from Radboud University Medical Center in Nijmegen, the Netherlands.

5. Financial report

- The Chairman presented the report of the Finance Sub-committee showing the balance sheet (income and expenditure) for 2009 and the budget for 2010. Both income (5,943,762 euro) and expenditure (5,945,504 euro) in 2009 were higher than budget, and showed a small negative balance of -1742 euro. The budget for 2010 sets a higher negative balance of -120,243 euro, mainly accounted for by continuing greater investment in the SIGs and Task Forces; SIG/TF expenditure is expected to reach 1,354,975 euro in 2010 (19% of total expenditure), with SIG/TF income budgeted at just 800,000 euro. The annual meeting continues to provide the Society's greatest source of income (67%) and expenditure (50%). The financial state of the Society was described as 'good', and the report was approved by the members.

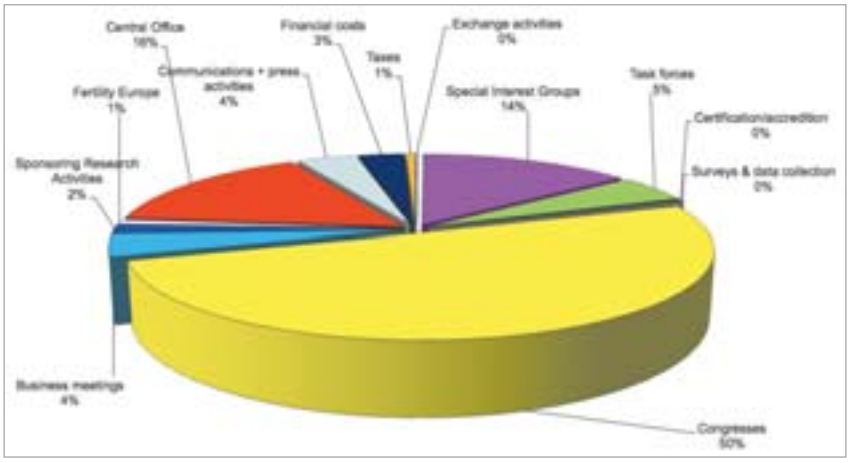
6. Membership of the Society

- Membership of the Society now stands at 5668, a further increase on last year, with almost 71% of members now coming from Europe. The top membership countries are Italy (350 members), UK (348), Netherlands (313), Spain (301), Germany (298) and USA (265). The greatest increase in membership in the past year has been from Asia (+ 26%) and Africa (+ 21%).
- Disciplines most prominently represented are reproductive endocrinology (1673 members) and embryology (1634 members), but there is strong membership growth in ethics and law and reproductive genetics

7. Any other business

- The Chairman noted the latest impact factors for the ESHRE journals, with *Human Reproduction Update* still leading the O&G field with 7.042. Both *Human Reproduction* and *MHR* continued to rise, the former at 3.859 and the latter at 3.005.

- The next General Assembly will be on 5th July 2011 in Stockholm at 18.00 pm.
- All slides presented at the General Assembly are available on the ESHRE website (www.eshre.eu).

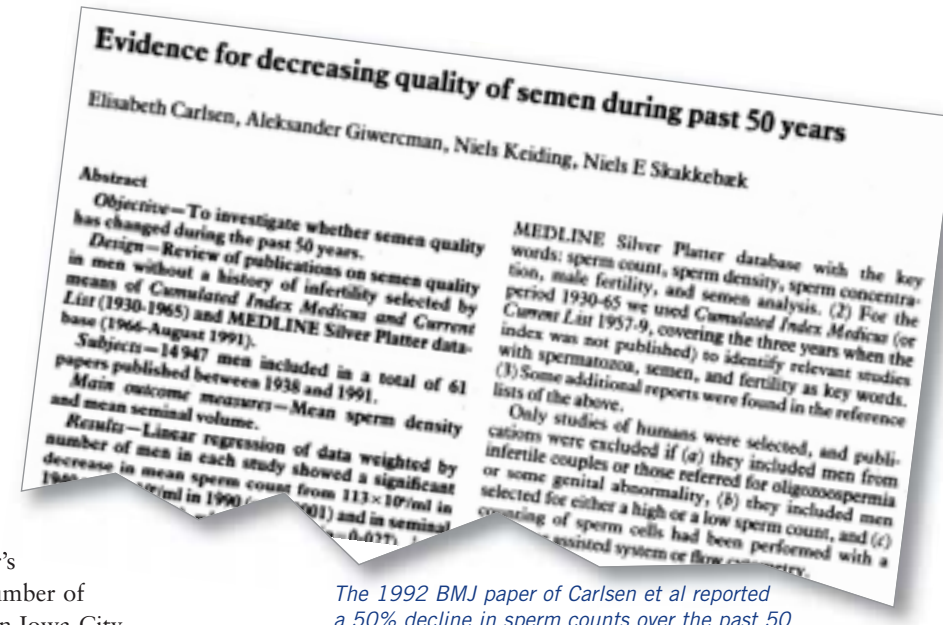


Where the money goes: ESHRE expenditure 2009.

Sperm quality

The clinical implications of environmental factors

Despite numerous studies, there is still no unequivocal evidence that sperm counts are falling - or that environmental and occupational toxins are the cause. Roelof Menkveld looks at the data, and concludes that a true reflection of sperm quality will only be derived from consistently applied standards of semen analysis.



Evidence for decreasing quality of semen during past 50 years

Elisabeth Carlsen, Aleksander Giwercman, Niels Keiding, Niels E Skakkebæk

Abstract

Objective—To investigate whether semen quality has changed during the past 50 years.

Design—Review of publications on semen quality in men without a history of infertility selected by means of Cumulated Index Medicus and Current List (1930-1965) and MEDLINE Silver Platter database (1966-August 1991).

Subjects—14 947 men included in a total of 61 papers published between 1938 and 1991.

Main outcome measures—Mean sperm density and mean seminal volume.

Results—Linear regression of data weighted by number of men in each study showed a significant decrease in mean sperm count from 113×10⁶/ml in 19[illegible]/ml in 1990 [illegible]001) and in seminal [illegible]-037).

MEDLINE Silver Platter database with the key words: sperm count, sperm density, sperm concentration, male fertility, and semen analysis. (2) For the period 1930-65 we used Cumulated Index Medicus (or Current List 1957-9, covering the three years when the index was not published) to identify relevant studies with spermatozoa, semen, and fertility as key words. (3) Some additional reports were found in the reference lists of the above.

Only studies of humans were selected, and publications were excluded if (a) they included men from infertile couples or those referred for oligozoospermia or some genital abnormality, (b) they included men selected for either a high or a low sperm count, and (c) counting of sperm cells had been performed with a [illegible]assisted system or flow [illegible]metry.

The 1992 BMJ paper of Carlsen et al reported a 50% decline in sperm counts over the past 50 years, and began a controversy over environmental effects which still continues today

In 1974 two American physicians from the corn belt of Iowa - Kinloch Nelson and Raymond G. Bunge - speculated that there might be a decreasing trend in human semen parameters, possibly the result of some adverse environmental factor to which the entire population was exposed.

This dramatic speculation arose from the pair's observation that there was an increase in the number of patients being referred to their infertility clinic in Iowa City. To investigate the observation, they studied semen specimens from a large number of men about to have vasectomies; Nelson and Bunge presumed that these were fertile men and representative of a normal population. They found their average sperm concentration to be 48 million/ml semen, which was significantly lower than the 107 million/ml semen of 1000 fertile men reported more than 20 years earlier by MacLeod and Gold in 1951.

A few years later in South Africa we found no evidence of a decreasing trend in the mean sperm concentrations of patients visiting our fertility clinic over a 15-year period between 1968 and 1982. However, we did observe a significantly decreasing trend in the mean percentage of morphological normal spermatozoa in the samples analysed. This decreasing trend was stronger in our non-white patient group (r = -0.4156) than in our white patient group (r = -0.3404).

We postulated that sperm morphology was a very sensitive semen parameter and that any adverse (eg, environmental) factor would first be reflected as a temporary decrease, and after repeated exposure as a permanent decrease in normal sperm morphology. The fact that the decrease was greater in our non-white patients was ascribed to the possibility that men from these groups were more exposed to adverse environmental conditions.[1]

However, it was only with the publication of Carlsen and colleagues' report in the *British Medical Journal* in 1992 ('Evidence for decreasing quality of semen during past 50 years') that controversy over the whole question of declining sperm quality really began.[2] Carlsen et al had sensationally suggested that sperm counts between 1940 and 1990 had fallen from a mean of 113 million/ml to a mean of 66 million/ml, a decline of around 50%. The report prompted a huge reaction.

Indeed, as recently as 2008 the New York urologist Harry Fisch, in a paper titled 'Declining worldwide sperm counts: disproving a myth', vehemently claimed that the approach of Carlsen and colleagues was misguided because the earlier publications in their review had included studies performed in North America, especially in the New York region now known for having a male population with higher mean sperm counts than found in other US cities; the data from the later periods were mainly from the European continent.[3] Behind Fisch's claims lay evidence of vast differences in mean semen values depending on continents, countries and even geographical regions within European countries. Thus, a reanalysis of the Carlsen data which excluded studies from the New York region showed no decline in sperm counts over the years.

Another criticism on the Carlsen study was that it included data from different heterogeneous population groups, including men who provided semen samples as donations to sperm banks, for infertility evaluation and IVF, and for pre-vasectomy analyses. Fisch argued that none of these populations represented a random sample of the population at large, with each different population presenting a selection bias - although some of these study populations are more likely to be biased than others.

Of greater concern than the question of decreasing semen parameters and male fertility, however, is the increasing incidence of testicular cancers, hypospadia and undescended testes, as has been reported in several papers in the wake of the Carlsen study and implicating the so-called endocrine disrupting compounds (EDCs) such as phthalates and pesticides.

It was claimed that the *in utero* exposure of the male foetus to estrogenic or anti-androgenic EDCs could cause disturbances in the development of the major cell types within the testis, including Sertoli cells. Such disturbances would then lead to decreased sperm counts (spermatogenic activity is determined by the number of Sertoli cells present in the tubuli) and an increasing incidence of testicular cancers, cryptorchidism and hypospadia. Moreover, it was proposed that the eating, smoking and drinking habits of mothers could also be a contributing factor to the lower semen qualities found in their sons.

The theory of EDCs was also questioned by Fisch. He

accepted that estrogenic compounds can be potent modulators of biochemical and physiologic functions in high doses, but doubted the implication that *in utero* or adult exposure to low levels of environmental EDCs could have any clinically detectable effects in humans.

However, there is growing evidence to suggest that, while a specific effect of a single toxic compound may not have a deleterious effect on the general population, a combination of several compounds may cause male genital malformations and reduced semen quality.

There is also ample evidence that the population of a localised area may be affected by adverse environmental conditions due to mining or certain chemical plant activities or, for instance, DDT spraying. Indeed, the effect of DDT is very evident in certain urban areas of South Africa, where DDT is still used for mosquito spraying and has been associated with decreased semen parameters in young men and significantly increased urogenital malformations in newborn boys.[4]

Such negative environmental influences may not only cause a temporary or permanent reduction in semen parameters but may also have an adverse effect on sperm DNA. With the use of different recently available tests, it has now been repeatedly shown that exposure to physical agents or chemicals, including therapeutic drugs and environmental toxins, can harmfully affect the integrity of sperm DNA chromatin, inducing structural, genetic and/or epigenetic abnormalities.

The mechanisms by which such damage is triggered are still largely unresolved and the susceptibility of each individual will depend on genetic background, lifestyle and exposure to various insults. However, depending on the nature of the chemicals, such environmental or occupational influences may directly target the DNA, induce oxidative stress or modify the epigenetic elements.[5]

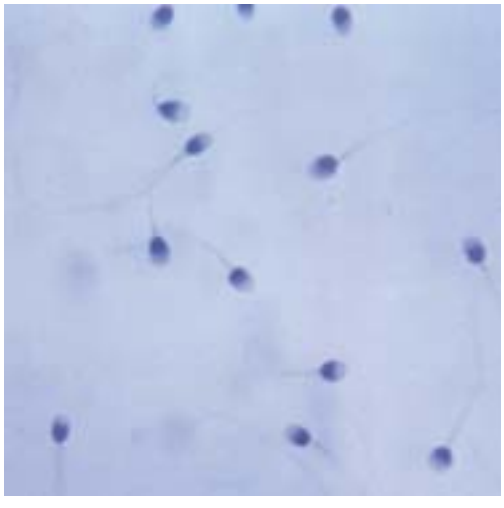
DNA integrity of the spermatozoon is of the utmost importance. After fertilisation of the oocyte, abnormal parental DNA has been associated with decreased pregnancy rates in ART, and proposed as a cause of idiopathic infertility. According to Delbès et al, it will be difficult to establish a direct link between paternal sperm chromatin integrity and the health of future generations, so it is essential to understand the impact of chemical and environmental factors on chromatin structure and epigenetic components of spermatozoa and their influence on further generations.[5]

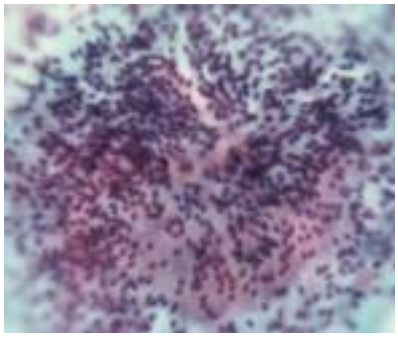
However, it's my view that for *in vivo* reproduction and pregnancy sperm DNA integrity may not be such an important determining factor. Strong selection against sperm with abnormal DNA takes place with the migration of spermatozoa through the endocervical mucus and with binding to the zona pellucida and it may be that the quality of our standard semen parameters are of more importance in the determination of a pregnancy. So where do we stand today regarding our current semen parameter qualities?

If recently published studies on semen parameters in fertile and subfertile populations are analysed, the mean sperm concentrations in the fertile populations are comparable to the 1990 mean of 66 million/ml semen as published in the Carlsen paper. Although the mean concentrations of the 'subfertile' populations published in these papers are considerably lower (see table), they are still (much) higher than the reference lower normal values of the new 2010 WHO semen analysis manual of 15 million spermatozoa/ml semen, progressive motility of 32% and morphological normal spermatozoa of 4%.

The new WHO values are also higher than the minimum values published by Van Zyl et al, who have reported in several articles since the 1970s a very low sperm concentration of >2.0 million/ml, >10% progressive motility and normal sperm morphology >3%.[6] These values are based on spontaneous pregnancies from our own patients in South Africa being investigated for infertility and from whom we obtained semen parameter data from analyses before and after the time of conception.

We should also ask if the observed declining trend in semen parameter values - if any - corresponds to a decrease in fertility as measured by human fecundity, especially in the light of the very low semen parameters needed for an *in vivo* pregnancy as noted above. According to te Velde et al, a reduction in human fecundity at the present moment can be neither confirmed or rejected because of the non-existence of an appropriate surveillance system.[7] In their opinion the only way to determine such a trend will be by the appropriate surveillance of total sperm counts (as a measure of male reproductive health) in combination with time to pregnancy (as a measure of couple fecundity) in carefully selected populations. Such studies, they suggest, must be started as soon as possible if we're looking for an answer on human fecundity in the next 20 to 30 years.





Strong selection against sperm with abnormal DNA takes place with the migration of spermatozoa through the endocervical mucus (left) and with binding to the zona pellucida (above).

Published data of spermatozoa concentrations (million/ml) in fertile and subfertile populations

Publication	Fertile population		Subfertile population	
	Mean (SD)	Range	Mean (SD)	Range
Ombelet et al, 1997	53.1	1.0 - 215.0	32.9	0.1 - 141.0
Zinaman et al, 2000	67.2 (47.8)	3.2 - 261.0	59.5 (53.7)[1]	3.0 - 234.0
Günalp et al, 2001	50.4 (32.0)	6.0 - 132.0	42.3 (27.4)	1.0 - 109.9
Guzick et al, 2001	67.0 (50.0)		52.0 (42.0)	
Menkveld et al, 2001	81.1 (49.7)	1.3 - 230.0	19.0 (26.5)[2]	0.3 - 130.0
Jedrzejczak et al., 2007	59.2 (27.5)	3.0 - 130.0	36.8 (25.6)	1.0 - 111.0

1= Non-pregnant group 2= Selected on an initial count <20 million/ml

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Menkveld R, Wong WY, Lombard CJ, et al. Semen parameters including WHO and strict criteria morphology, in a fertile and subfertile population: an effort towards standardisation of in vivo thresholds. Hum Reprod 2001; 16: 1165-1171.

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However, taking only sperm production and time to pregnancy as a measure of reproductive health may not be comprehensive enough. As I have suggested, sperm morphology may be a more sensitive tool for measuring testicular stress. The problem is, however, despite the WHO and NASA-ESHRE guidelines, that worldwide results from semen analyses and especially sperm morphology are not comparable because of the use of different techniques and interpretations of guidelines.

For sperm morphology to be of value, in a prospective study as proposed by te Velde et al, a central evaluation facility or co-operation between different facilities with very strict internal and external quality control is of the essence, as is the use of stored slides to ensure that decreasing values, if obtained, are not the result of a stricter application of the definition for normal.

It may also be useful to look at morphology patterns. Morphological abnormalities may be genetically determined or caused by stress (physiological, mental and environmental); the latter are reversible when the stress source is removed. As noted above, it may be that the testes can recuperate after an adverse attack or two, but after repeated episodes or continuous stress they may not self-repair - and permanently lower normal sperm morphology values may be the result.

The sentiment of te Velde et al is underlined by the view of Fisch, who proposes three strong reasons why a comprehensive re-evaluation of human male fertility is necessary: the potential impact of a real decline in semen quality and fertility is critical to human welfare; governments have begun to enact anti-EDC legislation which is partly based on selected portions of published data about semen quality; and confusion and misinformation about the possibility of decreasing semen quality remain widespread in lay and professional circles.

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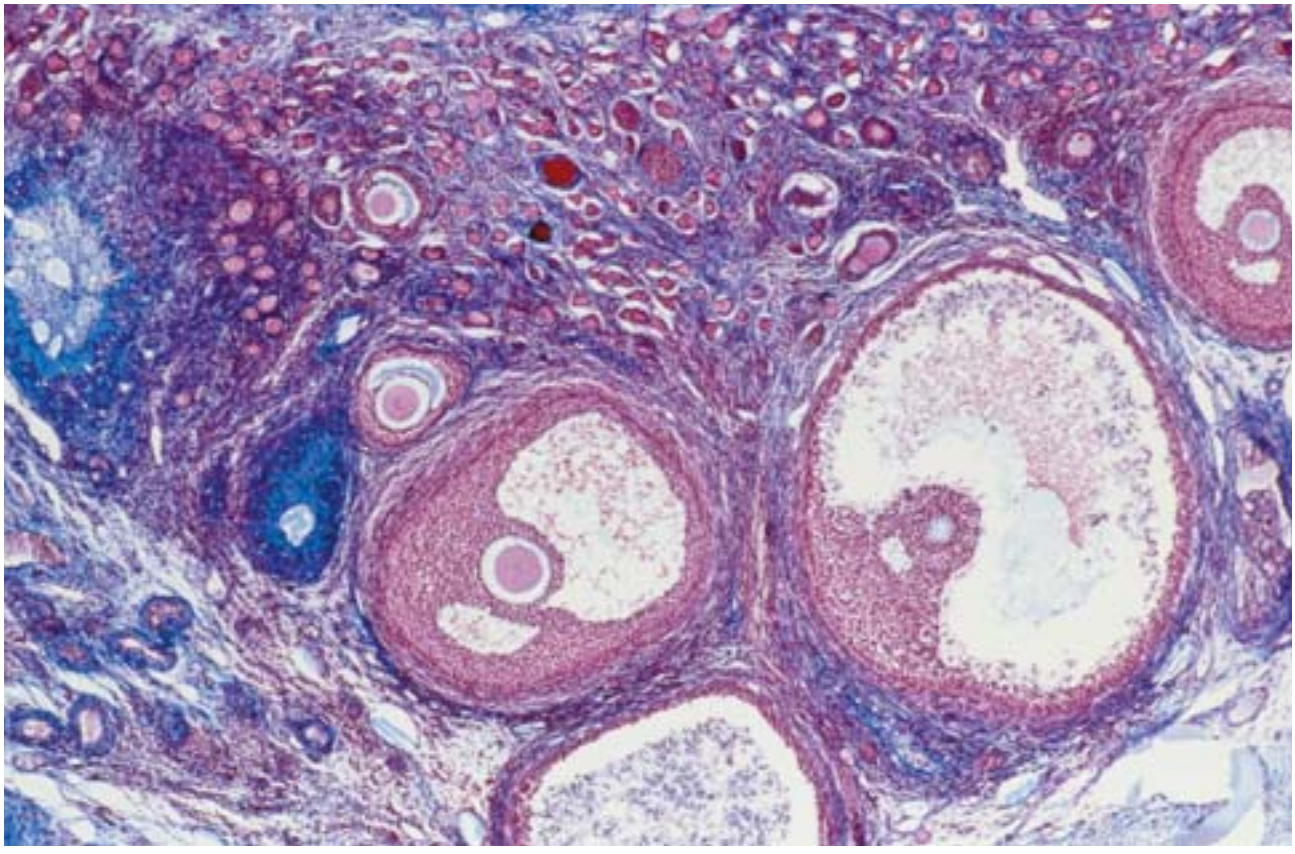


Tests of ovarian reserve

Juan Garcia-Velasco reviews their predictability in spontaneous and assisted conception

An indirect way to evaluate the reproductive age of a female patient is to perform one or several tests of ovarian reserve. Such tests aim to define the quantity - not the quality - of primordial ovarian follicles at a given age, and they are used widely both as screening tools and as diagnostic tests in women undergoing fertility treatment.

The tests are extremely important for providing adequate counselling of treatment outcome, and are very helpful in tailoring stimulation protocols because of their ability to discriminate between potentially low and high responders, or even predict cycle cancellation.

At our clinic in Madrid we have also found ovarian reserve tests useful in patients who have had previous oncological treatments or sparing ovarian surgery, for screening egg donors, and, last but not least, for plotting the fertility decline in women of advancing age. In such circumstances, therefore, tests of ovarian reserve seem to have an essential place in clinical decision-making, in preventing unnecessary treatment, and in providing reliable counselling to infertile couples.

But why have these tests become so important in recent years? The answer lies with the nature of our patients,

Biochemical markers
- FSH
- Estradiol
- Inhibin B
- AMH
- FSH:LH ratio

Morphometric markers
- Ovarian volume
- Antral follicle count
- Mean ovarian diameter

Dynamic markers
- Clomiphene citrate challenge test
- Exogenous FSH ovarian reserve test
- GnRH analogue stimulation test

and their gradual increase in age. We are seeing more and more couples planning to start their families at later ages, many when the female partner's ovaries are almost exhausted. Yet they are still socially and physically 'young' couples, and cannot understand why it's so difficult to have a baby in their early forties. In Madrid, for example, 68.6% of our 2047 fresh IVF cycles in 2009 were in women over the age of 34 - and in one-fifth of them we retrieved just four or fewer eggs; these were defined as our 'low responders'. Thus, realistic expectations need to be clear for these couples, and this is where we find tests of ovarian reserve extremely useful.

The tests can be grouped as biochemical, morphometric, and dynamic markers. The most popular are still basal hormones (FSH and estradiol) and the most promising antral follicle count (AFC) and anti-Mullerian hormone (AMH).

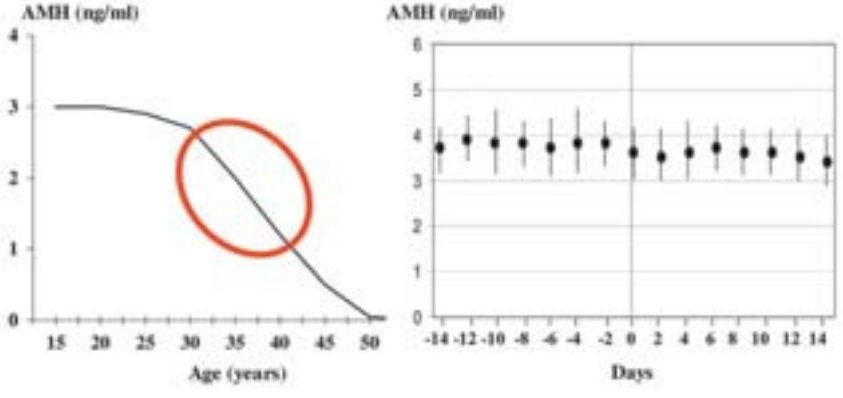
JUAN GARCIA-VELASCO: 'OOCYTE QUALITY CANNOT BE IMPROVED . . . AND WE CANNOT RECRUIT FOLLICLES THAT DO NOT EXIST'

Evidence is strong enough to say that the dynamic tests (clomiphene citrate challenge, GnRH agonist stimulation test, exogenous FSH ovarian reserve test) add very little benefit - if any - and their predictive accuracy is no better than that of biochemical or morphological markers.

Measuring cycle day 3 hormones (mainly FSH, but also estradiol, inhibin or even activin) is the most commonly used test for predicting ovarian response to ovarian stimulation in IVF. Hormone tests rely on the physiology of the menstrual cycle, but inter-cycle variability is not small, and this reduces reproducibility as well as usefulness.

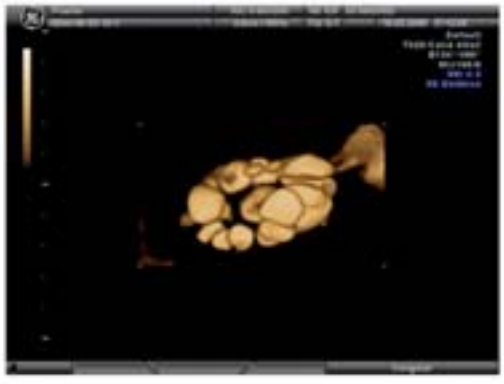
Almost 10 years ago it was shown in a meta-analysis of 21 studies that basal FSH is a moderate predictor of ovarian response, and absolutely non-predictive of pregnancy.[1] In fact, FSH has been found useless for excluding patients from treatment, as young and not so young patients are all able to achieve pregnancy regardless of their FSH levels; there's some evidence that the higher the FSH, the lower the chances of pregnancy, so FSH testing is useful for counselling but not to deny treatment.[2] When compared to age in a series of more than 1000 patients, it was shown that both FSH and age predict quantitative ovarian response in a similar fashion; however, age was a better predictor of pregnancy in IVF.

A very promising marker of ovarian response is AMH. This dimeric glycoprotein is secreted by granulosa cells in primary and pre-antral follicles, so its levels provide a good estimate of the healthy follicles still available for recruitment. Serum levels of AMH decline sharply with advancing maternal age, are not influenced by cycle day or previous hormonal treatments, and have only very minor intercycle variability. Thus, AMH seems to be a very precise and reliable marker of ovarian response, confirmed by recent evidence as a robust, consistent prognostic marker of ovarian response to stimulation;



Serum levels of AMH decline sharply with age and are not influenced by cycle day (after La Marca 2010).

'3D technology has not improved the sensitivity of conventional 2D ultrasonography for AFC measurement.'



however, the link to oocyte quality is still pending.

Among morphometric markers of ovarian reserve, antral follicle count has gained great popularity as well as scientific respect, especially when compared to other morphometric tests such as ovarian volume. Antral follicles, measuring from 2 to 8mm, are easily observed with the high-precision transvaginal ultrasound probes found today in any IVF clinic, and 3D technology has not improved the sensitivity of conventional 2D ultrasonography for AFC measurement. Any clinician can be easily trained in this highly reliable technique; it is simple, quick, accessible to all clinicians, and cheap.

When compared with the more trendy AMH as a marker of ovarian reserve, AFC measurement was shown in a recent meta-analysis of 11 trials to have a similar accuracy and ability to predict ovarian response to stimulation, although neither could predict pregnancy.[3] When the predictive ability of AFC was compared to FSH, a summary from 43 trials established that AFC performed better, was easier to use and was non-invasive, which is also an essential feature.[4]

The are two more points to be emphasised when counselling patients about their ovarian reserve: first, oocyte quality cannot be improved and is strongly related to age; and second, we cannot recruit follicles that do not exist.

Thus, we can conclude that day 3 FSH testing is interesting but has a high inter-cycle variability which minimises its validity as a prognostic marker; AMH is more robust, as it can be measured on any cycle day, with or without oral contraceptives, and with very low inter- as well as intra-assay variability; and AFC is a highly reliable and reproducible marker, with very low cost for patients. And, last but not least, age is the cheapest and only marker of oocyte quality.

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The specificity, sensitivity and features of the principal tests

		Specificity	Sensitivity	Main characteristics
Basal FSH	21 studies	90%	20%	* High intercycle variability
AFC	11 studies	40-98%	9-60%	* Performs better than FSH, highly reproducible, easily accessible, inexpensive
Ovarian volume	10 studies	71-100%	5-70%	* Lower predictive capacity than AFC
AMH	11 studies	50-96%	39-97%	* Performs similarly to AFC, little intercycle variability, highly reproducible, unaltered by cycle day or previous oral contraceptive use

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